

FOCUS: CLINICAL DECISION SUPPORT

# PREVENTING EXACERBATION OF AN ADE WITH AUTOMATED DECISION SUPPORT

## ABSTRACT

*This case demonstrates that, despite physician disregard of appropriate expert system warnings during computerized physician order entry, the distribution of alert "override" warnings to non-physician members of the clinical team can help avert adverse drug events.*

**WILLIAM L. GALANTER, MD, PHD, ROBERT J. DIDOMENICO, PHARM D, AND  
AUDRIUS POLIKAITIS, PH D**

**A**dverse drug events (ADEs) are receiving significant attention in the public media as well as in the medical literature. ADEs have been shown to contribute to the morbidity and mortality associated with the treatment of disease, as well as the cost of the care.<sup>1,2,3</sup> Many ADEs are preventable, with estimates in the literature ranging from 20 to 69 percent.<sup>1,4,5,6,7</sup> Preventable ADEs are often the result of medication errors, defined as errors in drug ordering, transcribing, dispensing, administering, or monitoring.<sup>8</sup>

Medication errors that adversely affect patient outcomes have been estimated to occur in 0.25 percent of all hospitalized patients.<sup>9</sup> The 1999 Institute of Medicine report raised awareness to the magnitude of this problem. This report estimated that ADEs related to medication errors resulted in tens of thousands of deaths annually.<sup>10</sup>

Therefore, efforts to reduce medication errors have the ability to lower the rate of ADEs substantially and improve the overall delivery of healthcare.

Information and knowledge offered to the clinician in order to facilitate the best decision and thereby reduce medication errors is termed clinical decision support (CDS). CDS can be completely manual, fully automated, or a mixture of technology and human intervention. Several studies have shown that employing clinical pharmacists as a form of CDS reduces medication errors and associated costs.<sup>11,12,13</sup> Chertow describes a fully automated approach to reducing medication errors at the time of computerized physician order entry (CPOE) in patients with impaired renal function.<sup>14</sup> A mixed system was described in a study by Raschke, in which computerized medication safety alerts were automatically generated to pharmacy professionals, who then manu-

## KEYWORDS

*Adverse drug events (ADEs)*

*Decision support*

*Computerized physician order entry*

*Alerts*

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ally communicated these alerts to physicians.<sup>15</sup>

The best method to communicate CDS generated alerts to practitioners has not been determined. As CPOE use becomes more prevalent in our healthcare system, it is likely that automated CDS systems will interact directly with practitioners during the ordering process. However, a broad spectrum of alerts may be generated outside of the ordering process related to recently reported abnormal laboratory results, recommendations made by consulting practitioners, or changes in the patient's clinical status as documented by the nursing staff. Therefore, additional methods of disseminating information generated by automated CDS systems must be considered in order to adequately communicate the potential for medication error to practitioners as well as to increase the likelihood of the most efficacious decision.

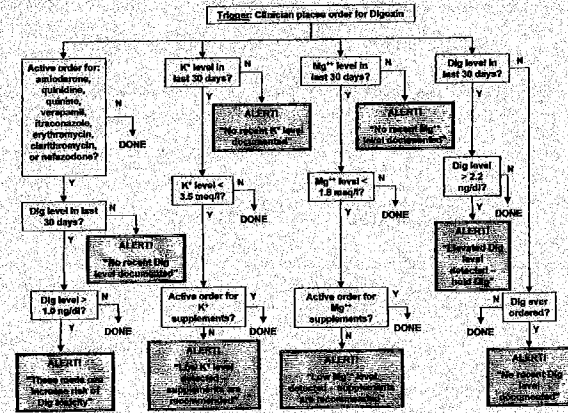
Establishing different tiers of safety alert communication to clinicians, based on the severity or acuity of the potential medication error may be preferable. If the potential for error or harm is less significant, a safety alert that simply warns the clinician of the potential for ADEs during the medication ordering process may be sufficient.

In situations where the potential for harm is more critical, a more advanced and aggressive safety alert may be helpful. Safety alerts of this type may have a default clinical action associated with them (e.g., discontinuation of a particular medication), forcing the practitioner to disregard or "override" the recommendation in order to proceed with the medication order.

In the event a practitioner "overrides" such an alert, the potential risk for medication error remains. Therefore, an escalation of the alert notification process may be necessary to inform other clinicians of the potential for medication error and resultant ADE. The "override" communication may take the form of a page, e-mail, phone call, or print-out, and may be dependent on the estimated severity of the potential medication error identified. This "override" communication may also transfer some of the responsibility for evaluating and preventing the potential medication error to each of the practitioners notified by the CDS system. As CDS systems are widely deployed, consideration must be given to the modes of communication and appropriate recipients that need to receive alert "override" warnings.

Digoxin is a drug used in the treatment of heart failure and supraventricular arrhythmias. This drug has a narrow therapeutic index, meaning that the drug level that is potentially harmful is not much higher than the level that is beneficial. While effective in treating these conditions, relatively minor changes in dose or clinical status of a patient may dramatically increase the potential for serious, even life-threatening toxicities. Studies have shown that

**Figure 1. Clinical decision support (CDS) system triggering events, logic, and resulting actions.**



Example of rule logic that generates real-time alerts while ordering digoxin for patients receiving potentially interacting drugs, with concomitant electrolyte abnormalities, or with elevated digoxin levels.

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the clinical and economic impact of digoxin toxicity can be worse than the underlying diseases it is used to treat.<sup>16,17,18</sup>

Adverse drug events with digoxin are, in most cases, the result of medication errors due to drug interactions, existing electrolyte abnormalities, lack of dosage adjustment in patients with renal insufficiency, or a combination of the three.<sup>16,18</sup> Because medication errors with digoxin are rather predictable, preventable, and can be easily identified through determination of elevated serum digoxin levels, digoxin is an excellent target for automated CDS as a means to prevent ADEs.

At the University of Illinois Medical Center at Chicago, we employ an automated CDS system that utilizes a variety of safety alerts and communication modes to warn clinicians of the potential for medication errors. The case described below demonstrates our multi-level CDS system, the utility of using various modes of communicating safety alerts to practitioners, and the limitations of such systems.

#### Case Example

**Clinical Decision Support System.** The hospital is an urban academic teaching institution with CPOE in use for over 10 years. The majority of the medication orders (66%) are placed directly by physicians, primarily resident

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physicians. Drug-drug and drug-allergy interaction checking is employed as a mandatory part of the ordering process. Patient allergies must be documented before the CPOE system allows placement of a medication order. In addition, a more sophisticated CDS (Discern Expert, Cerner Corporation) is employed. A suite of CDS rules was developed to assist physicians in prescribing digoxin more safely and appropriately warn of the potential for medication errors.

The digoxin CDS rules use patient-specific information maintained in the electronic medical record, including renal function assessments (serum creatinine, calculated creatinine clearance), serum electrolyte concentrations (potassium and magnesium), serum digoxin concentrations, and concomitant medication orders (e.g., amiodarone, quinidine, electrolyte supplementation, etc.) to identify potential medication errors associated with digoxin.

The CDS system can be evoked by ordering a medication (digoxin or interacting drug), in response to abnormal laboratory results that may precipitate digoxin toxicity, or in response to an "override" alert (described above). When a potential medication error is identified by the CDS system, safety alerts are communicated to the prescriber, warning of potential ADEs and suggesting ways to minimize or prevent them.

Communication of these safety alerts is done in several ways: directly to the prescriber at the time of order entry (real-time), via printout at designated nursing stations and inpatient pharmacies, and to an electronic clinical inbox (similar to e-mail) of designated providers caring for the patient. A schematic of the CDS system triggers, logic, and resulting alerts for ordering digoxin is illustrated in figure 1.

**Patient Case.** A 36-year-old woman with a past medical history of congestive heart failure, valvular heart disease, atrial flutter, and non-sustained ventricular tachycardia presented to the emergency department complaining of progressive shortness of breath over several months, worsening over the last few days prior to admission. She also complained of palpitations and chest pressure for one day. She was diagnosed with an acute exacerbation of congestive heart failure and atrial fibrillation with a rapid heart rate, ranging from 120 to 190 beats/minute. Basic laboratory tests revealed impaired renal function (serum creatinine 1.7 mg/dl, calculated creatinine clearance 38 ml/min), low serum magnesium, and low serum sodium. She weighed 58.2 kg (128 pounds).

In the emergency department, the patient was given digoxin 0.5 mg intravenously. This medication order was

written by hand, not ordered via CPOE, thus the computerized CDS system was not engaged during the order process. The patient was also treated with intravenous diltiazem and furosemide.

The patient was subsequently admitted to the telemetry unit. A subsequent order for digoxin 0.25 mg intravenously was ordered by the medical intern. During the ordering process, the ordering physician received three separate safety alerts warning of the potential for ADEs with digoxin: the first warned that the patient's low serum magnesium increases the risk of digoxin associated ADEs, the second warned that the patient's impaired renal function increases the risk of an elevated digoxin level, subsequently increasing the risk of a digoxin associated ADE, and the third alert warned that no recent assessments of the serum digoxin concentration had been performed, based on the knowledge of prior use of digoxin in this patient.

Examples of these alerts are shown in figure 2. In response to these safety alerts, the physician ordered a serum digoxin level for the following morning, but did not order magnesium supplementation as suggested.

A few hours later, the same physician ordered a third dose of digoxin, 0.25 mg intravenously, to complete a digoxin "loading" dose. The physician received the same safety alerts, warning of the low serum magnesium, impaired renal function, and no assessment of serum digoxin concentrations. The physician again failed to order magnesium supplementation.

The following morning, magnesium was ordered by another physician in response to the patient's low serum magnesium.

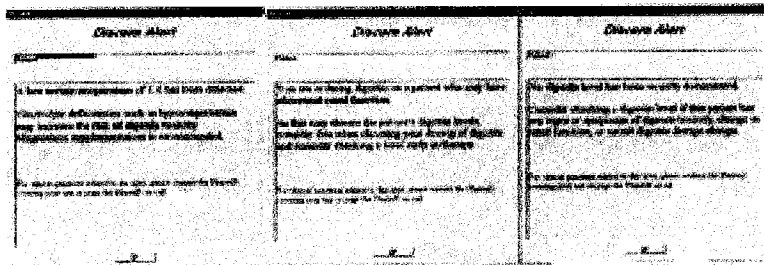
Laboratory results again revealed impaired renal function and an elevated serum digoxin concentration of 3.3 ng/ml (normal range <2.2 ng/ml). The patient was experiencing symptomatic bradycardia (heart rate 59 beats/minute). The elevated digoxin concentration triggered the automated CDS system, resulting in a printed warning at the designated pharmacy and nursing station. Notice of this elevated digoxin concentration was also forwarded to the clinical inbox of all physicians and pharmacists caring for the patient.

In response to the generated alerts, follow-up from pharmacy and nursing was initiated, and the digoxin order was discontinued. Several hours later, a physician ordered digoxin 0.25 mg orally as a maintenance dose. This order triggered another safety alert warning for poor renal function, and strongly advised against ordering more digoxin due to the recently posted elevated serum digoxin level. Based on advice from a supervising physician, the physician disagreed with this alert recommendation, "overrode"

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Figure 2. Alert examples



Real-time alerts that appear when digoxin is ordered for a patient with low serum magnesium level, impaired renal function, and no recent assessment of serum digoxin concentration.

the default alert action that would have cancelled the order, and proceeded with the order for digoxin.

The act of "overriding" the alert recommendation initiated mechanisms to notify other clinicians of the potential for digoxin ADEs in this patient. Subsequently, safety alerts were printed in the pharmacy and at the nursing station and were also forwarded to the electronic clinical inbox of the patient's designated healthcare providers. In response to this alert "override" warning, a pharmacist intervened and initiated a discussion with the physician regarding the existing ADE and the high risk of exacerbation if the digoxin order was continued. Digoxin was ultimately discontinued before the patient could receive subsequent doses.

The patient's symptoms gradually resolved and her serum digoxin concentration decreased to 1.8 ng/ml the following morning. The patient was eventually discharged on the fourth day of admission. It is unlikely that this ADE caused any permanent harm to the patient or increased her length of stay.

#### Discussion

**Case Analysis.** This case demonstrates that ADEs can still occur despite the use of CPOE and CDS systems. In the case reported here, an ADE associated with digoxin did occur (symptomatic bradycardia); however, exacerbation of this ADE was likely prevented by the automated CDS system and the human interaction of qualified healthcare providers. The etiology of this ADE was likely multifactorial. The bradycardia and supratherapeutic digoxin levels were dose-related, but concomitant drug therapy (diltiazem) likely contributed as well.

The pharmacokinetics and pharmacodynamics of digoxin are well understood. Digoxin has an elimination half-life of 1.6 days, the kidneys being the primary elimination route.<sup>19</sup>

Because of the prolonged half-life, digoxin is often given as a "loading dose" to rapidly increase serum concentrations followed by a maintenance dose to maintain steady-state digoxin concentrations. While there are several methods of determining an appropriate loading dose of digoxin, the method described by Jelliffe and Brooker is generally regarded as the standard; the dose is 10-15 mcg/kg, given as two or three divided doses, each six hours apart from one another.<sup>20</sup>

Maintenance doses are dependent upon a patient's weight and renal function. Patients weighing less or who may have renal impairment

require smaller maintenance doses compared to larger patients or those with normal renal function. Our patient was given a total 1,000 mcg (17 mcg/kg) as a loading dose, higher than that recommended by Jelliffe, resulting in supratherapeutic digoxin concentration and contributing to her ADE. Because our patient also had renal insufficiency, the prescribed maintenance dose (0.25 mg) was more than that recommended for someone with her degree of renal insufficiency.

The CDS system at the University of Illinois warns clinicians when renal insufficiency is present in patients prescribed digoxin, suggesting dosage adjustment to reduce the potential for ADEs. In addition, it warns clinicians when electrolyte abnormalities (e.g., low serum potassium, low serum magnesium) and drug interactions (e.g., amiodarone, quinidine, etc.) are present.

However, in the case presented here, the automated CDS failed to prevent the ADE for two reasons.

The initial care of the patient occurred in the emergency department, where medication orders are performed verbally or in writing (not performed with CPOE), and the medication is dispensed without prior review by a pharmacist. Thus, any efforts to provide automated or human CDS were circumvented. CPOE, coupled with a computerized CDS system,

would have been useful in this setting as suggested by our case. Additionally, our CDS system presently does not perform dose checking and, therefore, the large weight-based digoxin loading dose was not detected.

Once the patient was admitted to the hospital and medication orders were performed via CPOE, the CDS system was able to provide warnings to the ordering physicians, suggesting digoxin ADEs were a risk in this patient (she had

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low serum magnesium and renal insufficiency) and providing recommendations to avoid these potential ADEs. In the development of our CDS system, we designed a hierarchy of alerts, based on the perceived risk and severity of possible ADEs. In the case of digoxin, for those situations where the perceived risk or severity of ADEs is least severe (e.g., electrolyte abnormalities, etc.), the safety alerts are largely informative and suggest, but do not require, further action.

In the described case when ordering digoxin for the patient, the physician was warned twice that low serum magnesium was present, suggesting magnesium supplementation, but the physician decided this was unnecessary at the time. In situations where the ADE risk is greater (e.g., supratherapeutic digoxin concentrations in patients with current orders for digoxin), the alert is more broadly distributed, notifying several healthcare providers by printouts and clinical inbox. In our patient, when the toxic digoxin concentration was detected, printouts in pharmacy and the nursing unit as well as electronic notifications were generated, resulting in the discontinuation of the current digoxin order.

For instances where the ADE risk is considered to be very high (e.g., placing new orders for digoxin in patients with toxic digoxin concentrations), we designed the safety alerts to automatically discontinue the proposed medication order. To proceed with such an order, the ordering clinician must "override" the default action (e.g., discontinue digoxin), prompting the simultaneous notification of several providers and requiring appropriate follow-up prior to dispensing and administration of the ordered medication.

In our patient case, this "override" notification was generated when the maintenance dose of digoxin was ordered in the presence of toxic digoxin levels despite warnings and a default action to the contrary. The goal of this safety alert escalation is to inform several other practitioners and initiate human interaction to resolve the potential problem. In the case described above, the interaction between pharmacist and physician led to the discontinuation of digoxin and prevented exacerbation of an ADE.

**Communication of Alerts.** The communication of alerts generated by CDS systems to healthcare practitioners has received some attention in the literature. Specifically, two questions seem to be continually addressed: who should be notified of the CDS alerts and how they should be notified. Certainly in the context of computer physician order entry, CDS systems are expected to interact directly with practitioners during the actual process of ordering. However, the effective communication of asynchronous alerts generated outside of the ordering process does require additional consideration.

The benefit of alerting healthcare practitioners to recent critical laboratory results in a timely manner has been substantiated<sup>21,22,23,24</sup> and associated strategies for conveying such alerts have evolved. Tate initially displayed alert information to anyone who reviewed the patient's laboratory data.<sup>21</sup> A flashing light at the nursing station was even considered as a means to decrease the alert acknowledgement time.<sup>25</sup> Rind sent e-mails to any practitioner who had recently reviewed the patient's clinical data.<sup>23</sup> More recently alerts have been communicated to healthcare practitioners via pager or other wireless devices.<sup>26,27,28,29</sup>

Ideally the information should be communicated directly to the patient's covering physician; however, tracking the identity of this practitioner can be quite a challenge. Efforts to maintain appropriate patient-provider relationships have largely been based on the maintenance of individual and group call-schedules.<sup>29,30</sup> A recent proposal endorses provider self-identification within the daily clinical workflow of signing out patients as the most effective means to maintain accurate relationships.<sup>31</sup>

However, the optimal communication of "override" warnings has received little attention. Suitable answers to the fundamental questions of who should be notified and how they should be notified are more critical given that this class of asynchronous alerts may indicate potential for serious human-error induced patient harm. "Override" warnings would be completely unnecessary if clinical information systems mandated conformance to established care practices and did not allow for aberrant practitioner behavior.

However, in our view, with rare exceptions, system-imposed restrictions on clinician behavior are inappropriate. Clinical circumstances may require a practitioner to disregard established care practices. It is unlikely that system designers could consider every possible clinical circumstance and, therefore, practitioners must be given the freedom to act on their best clinical judgment, after being provided with all relevant clinical information and alerts as necessary. However, notifying other practitioners of clinical actions contrary to accepted practices and with high potential for an adverse event may be beneficial.

As described in this case study, the strategy of broadly communicating the "override" warning successfully prevented the further exacerbation of a medication error and a subsequent ADE. In situations where the potential for harm is more critical, the use of "override" warnings and their ensuing communication to appropriate providers should be given further consideration as another component of a clinical decision support patient safety strategy.

### Conclusions

Although only an anecdotal report, this case demonstrates the benefit of two elements of an automated CDS system. This first is the ability of a CDS system to identify those clinician responses to alerts that do not conform with the alert recommendations and suggested actions in situations where the potential harm to patients is great. The second is the distribution of safety alerts to multiple providers in addition to the ordering clinician to increase the likelihood that appropriate action will be taken to prevent ADEs.

Although well intentioned, the physician's use of digoxin was not consistent with the standard of care and placed the patient at high risk of an ADE. The subsequent communication to the pharmacy and nursing staff led to a discontinuation of the drug, and prevented an exacerbation of an ADE already in progress. As automated CDS systems evolve and become more common, formal analyses evaluating their success and the most effective methods for providing CDS will be necessary.

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**About the Authors**

William Galanter, MD, PhD, is a clinician/educator at the University of Illinois Hospital and is the physician liaison to the electronic medical record implementation project from the Department of Medicine. He is chair of the automated decision support committee.

Robert DiDomenico, PharmD, is a clinical assistant professor at the University of Illinois at Chicago College of Pharmacy and a clinical pharmacist at the University of Illinois Hospital. He is an expert in cardiovascular pharmacology and a member of the automated decision support committee.

Audrius Polikaitis, PhD, is a product manager at Cerner Corporation, Kansas City, Missouri, focusing on the development, deployment, and utilization of clinical decision support systems.

**References**

- <sup>1</sup>Bates, D. W., Spell, N., Cullen, D. J., et al. "The Costs of Adverse Drug Events in Hospitalized Patients." *Journal of the American Medical Association*, 1997, 277(4), 307-311.
- <sup>2</sup>Classen, D. C., Pestotnik, S. L., Evans, S., et al. "Adverse Drug Events in Hospitalized Patients." *Journal of the American Medical Association*, 1997, 277(4), 301-306.
- <sup>3</sup>Johnson, J. A., and Bootman, J. L. "Drug-Related Morbidity and Mortality: A Cost-of-Illness Model." *Archives of Internal Medicine*, 1995, 155(18), 1949-1956.
- <sup>4</sup>Bates, D. W., Boyle, D. L., Vander Vliet, M. D., et al. "Relationship Between Medication Errors and Adverse Drug Events." *Journal of General Internal Medicine*, 1995, 10, 199-205.
- <sup>5</sup>Bates, D. W., Cullen, D., Laird, N., et al. "Incidence of Adverse Drug Events and Potential Adverse Drug Events; Implications for Prevention." *Journal of the American Medical Association*, 1995, 274, 29-34.
- <sup>6</sup>Bates, D. W., Leape, L. L., and Petrycki, S. "Incidence and Preventability of Adverse Drug Events in Hospitalized Adults." *Journal of General Internal Medicine*, 1993, 8, 289-94.
- <sup>7</sup>Leape, L. L., Lawthers, A. G., Brennan, T. A., and Johnson, W. G. "Preventing Medical Injury." *Quality Review Bulletin*, 1993, 19, 144-9.
- <sup>8</sup>Kaushal, R., Bates, D. W., Landrigan, C., et al. "Medication Errors and Adverse Drug Events in Pediatric Patients." *Journal of the American Medical Association*, 2001, 285, 2114-20.
- <sup>9</sup>Bond, C. A., Raehl, C. L., and Franke, T. "Medication Errors in United States Hospitals." *Pharmacotherapy*, 2001, 21, 1023-36.
- <sup>10</sup>*To Err Is Human: Building a Safer Health System*. Washington, DC: National Academy Press, 1999.
- <sup>11</sup>Katona, B. G., Ayd, P. R., Walters, J. K., Caspi, M., and Finkelstein, B. W. "Effect of a Pharmacist's and a Nurse's Interventions on Cost of Drug Therapy in a Medical Intensive Care Unit." *American Journal of Hospital Pharmacy*, 1989, 46, 1179-82.
- <sup>12</sup>Leape, L. L., Cullen, D. J., Clapp, M. D., et al. "Pharmacist Participation on Physician Rounds and Adverse Drug Events in the Intensive Care Unit." *Journal of the American Medical Association*, 1999, 282, 267-70.
- <sup>13</sup>Bond, C. A., Raehl, C. L., and Franke, T. "Clinical Pharmacy Services, Hospital Pharmacy Staffing, and Medication Errors in United States Hospitals." *Pharmacotherapy*, 2002, 22, 134-47.
- <sup>14</sup>Chertow, G. M., Lee, J., Kuperman, G. J., et al. "Guided Medication Dosing for Inpatients with Renal Insufficiency." *Journal of the American Medical Association*, 2001, 286, 2839-44.
- <sup>15</sup>Raschke, R. A., Gollhare, B., Wunderlich, T. A., et al. "A Computer Alert System to Prevent Injury from Adverse Drug Events." *Journal of the American Medical Association*, 1998, 280(15), 1317-1320.
- <sup>16</sup>Kelly, R. A., and Smith, T. W. "Recognition and Management of Digitalis Toxicity." *American Journal of Cardiology*, 1992, 69, 108G-19G.
- <sup>17</sup>Roberts, S. A., Diaz, C., Nolan, P. E., et al. "Effectiveness and Costs of Digoxin Treatment for Atrial Fibrillation and Flutter." *American Journal of Cardiology*, 1993, 72, 567-73.
- <sup>18</sup>Gandhi, A. J., Vlasses, P. H., Morton, D. J., and Bauman, J. L. "Economic Impact of Digoxin Toxicity." *Pharmacoeconomics*, 1997, 12, 175-81.
- <sup>19</sup>Jelliffe, R. W. "A Mathematical Analysis of Digitalis Kinetics in Patients with Normal and Reduced Renal Function." *Mathematical Bioscience*, 1967, 1, 305-25.
- <sup>20</sup>Jelliffe, R. W., and Brooker, G. "A Nomogram for Digoxin Therapy." *American Journal of Medicine*, 1974, 57, 63-8.
- <sup>21</sup>Tate, K. E., Gardner, R. M., and Weaver, L. K. "A Computerized Laboratory Alerting System." *MD Computing*, 1990, 7(5), 296-301.
- <sup>22</sup>Kuperman, G. J., Teich, J. M., Tanasijevic, M. J., Ma'Luf, N., Rittenberg, E., Jha, A., Fiskio, J., Winkelman, J., and Bates, D. W. "Improving Response to Critical Laboratory Results with Automation: Results of a Randomized Controlled Trial." *Journal of American Medical Informatics Association*, 1999, 6(6), 512-22.
- <sup>23</sup>Rind, D. M., Safran, C., Phillips, R. S., Wang, Q., Calkins, D. R., Delbanco, T. L., Bleich, H. L., and Slack, W. V. "Effect of Computer-Based Alerts on the Treatment and Outcomes of Hospitalized Patients." *Archives of Internal Medicine*, 1994, 154(13), 1511-7.
- <sup>24</sup>Shabot, M. M., LoBue, M., Leyerle, B. J., and Dubin, S. B. "Decision Support Alerts for Clinical Laboratory and Blood Gas Data." *International Journal of Clinical Monitoring and Computing*, 1990, 7(1), 27-31.
- <sup>25</sup>Bradshaw, K. E., Gardner, R. M., and Pryor, T. A. "Development of a Computerized Laboratory Alerting System." *Computer and Biomedical Research*, 1989, 22(6), 575-87.
- <sup>26</sup>Tate, K. E., Gardner, R. M., and Scherting, K. "Nurses, Pagers, and Patient-Specific Criteria: Three Keys to Improved Critical Value Reporting." *Proceedings of the Annual Symposium on Computer Applications in Medical Care*, 1995, 164-8.
- <sup>27</sup>Kuperman, G. J., Teich, J. M., Bates, D. W., Hiltz, F. L., Hurley, J. M., Lee, R. Y., and Paterno, M. D. "Detecting Alerts, Notifying the Physician, and Offering Action Items: A Comprehensive Alerting System." *Proceedings of the AMIA Annual Fall Symposium*, 1996, 704-8.
- <sup>28</sup>Shabot, M. M., and LoBue, M. "Real-time Wireless Decision Support Alerts on a Palmtop PDA." *Proceedings of the Annual Symposium on Computer Applications in Medical Care*, 1995, 174-7.
- <sup>29</sup>Eisenstadt, S. A., Wagner, M. M., Hogan, W. R., Pankaskie, M. C., Tsui, F. C., and Wilbright, W. "Mobile Workers in Healthcare and Their Information Needs: Are 2-Way Pagers the Answer?" *Proceedings of the AMIA Symposium*, 1998, 135-9.
- <sup>30</sup>Hiltz, F. L., and Teich, J. M. "Coverage List: A Provider-Patient Database Supporting Advanced Hospital Information Services." *Proceedings of the Annual Symposium on Computer Applications in Medical Care*, 1994, 809-13.
- <sup>31</sup>Kannry, J., and Moore, C. "MediSign: Using a Web-based SignOut System to Improve Provider Identification." *Proceedings of the AMIA Symposium*, 1999, 550-4.

## Focus on Electronic Prescribing

## Research Paper ■

## A Trial of Automated Safety Alerts for Inpatient Digoxin Use with Computerized Physician Order Entry

WILLIAM L. GALANTER, MD, PhD, AUDRIUS POLIKAITIS, PhD, ROBERT J. DiDOMENICO, PHARM D

**Abstract** **Objective:** Automated clinical decision support (CDS) has shown promise in improving safe medication use. The authors performed a trial of CDS, given both during computerized physician order entry (CPOE) and in response to new laboratory results, comparing the time courses of clinician behaviors related to digoxin use before and after implementation of the alerts.

**Design:** Alerts were implemented to notify of the potential risk from low electrolyte concentrations or unknown digoxin or electrolyte concentrations during CPOE. Alerts were also generated in response to newly reported hypokalemia and hypomagnesemia in patients given digoxin.

**Measurements:** Clinician responses to the alerts for six months were compared with responses to similar situations for six months prior to implementation.

**Results:** During CPOE, checking for unknown serum values increased after implementation compared with control at one hour: 19% vs. 6% for digoxin, 57% vs. 9% for potassium, and 40% vs. 12% for magnesium as well as at 24 hours ( $p < 0.01$  for all comparisons). Electrolyte supplementation increased with newly reported hypokalemia and hypomagnesemia after implementation at one hour: 35% vs. 6% and 49% vs. 5% for potassium and magnesium, respectively, as well as at 24 hours ( $p < 0.01$  for all comparisons). During CPOE, supplementation for hypokalemia was not improved, whereas supplementation for hypomagnesemia improved at one hour ( $p < 0.05$ ).

**Conclusion:** Overall, the alerts improved the safe use of digoxin. During CPOE, alerts associated with missing levels were effective. For hypokalemia and hypomagnesemia, the alerts given during CPOE were not as effective as those given at the time of newly reported low electrolytes.

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Adverse drug events (ADEs) have been shown to contribute to the morbidity and mortality associated with the treatment of disease and the cost of the care.<sup>1-3</sup> Many ADEs are preventable, with estimates in the literature ranging from 20%

to 69%.<sup>4-7</sup> Preventable ADEs are often the result of medication errors, defined as errors in drug ordering, transcribing, dispensing, administering, or monitoring.<sup>8</sup> Medication errors that adversely affect patient outcomes have been estimated to occur in 0.25% of all hospitalized patients.<sup>9</sup> Therefore, efforts to reduce medication errors have the ability to lower the rate of ADEs substantially and improve the overall delivery of health care.

Affiliations of the authors: Section of General Internal Medicine, College of Medicine, University of Illinois at Chicago, Chicago, IL (WLG); University of Illinois Hospital, Chicago, IL (AP); Department of Pharmacy Practice, College of Pharmacy, University of Illinois at Chicago, Chicago, IL (RJD).

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Correspondence and reprints: William L. Galanter, MD, PhD, Department of Medicine, Section of General Internal Medicine (M/C 718), University of Illinois at Chicago, 840 South Wood Street, Chicago, IL 60612; e-mail: <billg@uic.edu>.

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Information and knowledge offered to the clinician to facilitate the best decision and thereby reduce medication errors are termed clinical decision support (CDS). Automated CDS systems transform clinical data gathered in an electronic medical record (EMR) as well as expert- or evidence-based practice guidelines into useful patient-specific knowledge to assist clinical decision making. Recent studies demonstrate that computerized physician order entry (CPOE) in conjunction with basic CDS such as drug-allergy and drug-drug interaction checking decreases the likelihood of serious medication errors.<sup>10,11</sup>

As CPOE use becomes more prevalent in our health care system, it is likely that clinicians will increasingly interact

directly with automated CDS systems at the time of, or synchronous to, the ordering process, providing alerts or information directly to the clinician during ordering. However, alerts may also be generated asynchronously to the ordering process, typically related to recently reported abnormal laboratory results.

In settings without CPOE, decision support alerts must be communicated after, or asynchronous to, the ordering process. Although there is a growing set of data regarding the utility of CDS in affecting clinician behavior,<sup>11-13</sup> there is a need to understand the comparative efficacy of synchronous alerts associated with CPOE compared with asynchronous alerts that have been used more commonly in the past. An understanding of the efficacy of these different types of alerts will be important in the design of future CDS systems.

Digoxin is a drug used in the treatment of heart failure and common supraventricular arrhythmias, particularly atrial fibrillation. Although effective in treating these conditions, relatively minor changes in the dose or clinical status of a patient may dramatically increase the potential for serious, even life-threatening toxicities. Studies have shown that the clinical and economic impact of digoxin toxicity can be worse than the underlying diseases that it is used to treat.<sup>14-16</sup> ADEs associated with digoxin are, in most cases, the result of medication errors due to drug interactions, existing electrolyte abnormalities, lack of dose adjustment in patients with renal insufficiency, or a combination of all three.<sup>14,16</sup> Thus, these adverse events are often predictable and preventable. Appropriate measurement and awareness of digoxin levels, electrolyte concentrations, and renal function minimize the risk of digoxin toxicity. Because the safe use of digoxin is guided, in part, by these quantifiable parameters, it is an excellent target for automated CDS as a means to prevent medication errors and ADEs.<sup>17</sup>

Our study simultaneously examined both synchronous and asynchronous alerts associated with inpatient use of digoxin. Because one of the potential promises of synchronous alerts in CPOE is a rapid response, we performed a trial of CDS alerts comparing the time courses of clinician behaviors related to the use of digoxin before and after implementation of the alerts. The efficacies of the synchronous and asynchronous alerts, as measured in this trial, can then be contrasted.

## Methods

### CPOE and CDS Environment

The University of Illinois Hospital and Medical Center utilizes a commercially available EMR (Millennium; Cerner Corporation, Kansas City, MO), which is used as the primary source of presentation of all results and orders to clinicians. All medication and laboratory orders are placed using CPOE, predominantly by resident physicians. The commercially available automated CDS (Discern Expert, Cerner Corporation) has been previously described.<sup>17,18</sup>

### Development of CDS Alerts

A decision support committee consisting of physicians, clinical pharmacists, nurses, information technology personnel, and a Cerner Corporation consultant developed decision support rules to promote the safe use of digoxin. The rules use patient-specific information maintained in the EMR, including potassium and magnesium concentrations, digoxin

concentrations, and concomitant medication orders (e.g., amiodarone, quinidine, electrolyte supplementation) to identify potential medication errors associated with digoxin. The standards for clinician behavior were determined by the committee based on both evidence in the literature and knowledge of prior ADEs at our own institution.<sup>16</sup> Although it is well known that renal dysfunction plays a large role in digoxin toxicity,<sup>14,16</sup> decision support addressing renal function was not available at the time of the study and was therefore not examined.

### Synchronous Alerts

The CDS system can be evoked by ordering a medication (digoxin or interacting drug) or in response to abnormal laboratory results that may increase the risk of digoxin toxicity. When digoxin is ordered using CPOE, the CDS interrogates discrete laboratory values within the EMR to ascertain the existence of specific clinical conditions: untreated hypokalemia or hypomagnesemia ( $K^+ < 3.5$  mEq/L or  $Mg^{2+} < 1.8$  mEq/L and without an order for electrolyte replacement), no recent assessment of a digoxin level in patients with prior digoxin use, a digoxin level  $> 2.2$  mg/dL in the past 30 days, and the concurrent use of medications known to increase the digoxin level. If any of these clinical conditions are identified, a real-time alert is presented to the ordering clinician, synchronous to the ordering activity. The alert is a pop-up box that is only informational and does not require a response or include the ability to produce an order automatically. The alert suggests the most likely appropriate action for the given clinical scenario; for instance, for hypokalemia, the alert suggests giving the patient potassium supplementation. Images of these alerts have been previously published.<sup>17</sup>

### Asynchronous Alerts

The CDS system can also be evoked in response to abnormal laboratory results that may increase the risk of digoxin toxicity. This asynchronous decision support is employed when a new potassium, magnesium, or digoxin level is posted to the EMR. The CDS considers the new result as well as the patient's concomitant medication orders and, if necessary, generates alerts warning of untreated hypokalemia or hypomagnesemia or elevated digoxin levels in patients receiving digoxin. The alerts are communicated via printout at designated nursing stations and inpatient pharmacies and sent to the electronic clinical inbox of designated clinicians, which had previously self-declared a clinical relationship with the patients when opening the patient-specific EMR. There is no limit to the number of designated clinicians. Typical examples of these clinicians are attending physicians, housestaff, consulting physicians, and pharmacists, among others, but not nurses. The distribution of the printed asynchronous alerts is based on patient location. The printed alerts contain instructions for both clerical staff and nurses regarding communication of the alert content to clinicians able to act on the alert.

### Chart Review for Determination of Alert Compliance

Patient charts were reviewed over a six-month study period to determine whether and when a clinician took appropriate action in response to an alert. This chart review was approved by our institutional review board. Only alerts warning of untreated hypokalemia or hypomagnesemia and no recent

digoxin, magnesium, or potassium levels were reviewed for alert compliance because these occurred with sufficient frequency and had clearly defined, appropriate clinician responses to allow analysis. The situations evaluated in this study and the corresponding expected clinician actions are described in Table 1. Although the charts and alerts were identified electronically, manual review was used to measure clinician responses.

A historical cohort was established for the six-month period prior to CDS digoxin alert implementation. For this historical control group, the EMR and an automated searching algorithm were used to identify alerting situations that would have generated an alert if the CDS alerts had been functioning at that time. This algorithm searched through all patients admitted to the hospital during the control period. Identical to the postalert period, manual chart review was used to establish a control rate of clinician responses. The historical control period was from February 15, 2001, through September 7, 2001, and the study period was from September 8, 2001, through March 31, 2002.

Time to clinician action was the primary metric of interest. This time was determined in the same way for the study and control groups. For the synchronous CDS alerts, the time to clinician action was defined as the time between placement of the digoxin order and the appropriate clinician response, if any. For the asynchronous CDS alerts, the time to clinician action was the time between the availability of new results in the EMR and the appropriate clinician response to the clinical situation, if any. Clinician responses were tracked for 24 hours. These response curves are essentially survival curves, typically used in clinical trials. Use of survival curves to measure the effectiveness of alerts has been suggested in the past by Rind et al.<sup>19</sup>

### Statistical Analysis

Kaplan-Meier survival curves were developed describing the proportion of patients with appropriate clinician action taken in response to an alert (or alerting situation) as a function of time. If no clinician action was taken, alerts were censored at 24 hours. These compliance curves were tested for equality using the log-rank statistic.

The proportion of patients for whom an appropriate clinician action occurred was also evaluated at both one and 24 hours, representing both short- and long-term responses to the alerts. This comparison of proportions utilized the  $\chi^2$  statistic or Fisher's exact test when  $n$  was less than 25.

Table 1 ■ Alerting Situations and Expected Actions

Alerting Situation	Expected Clinician Action
K <sup>+</sup> <3.5 mEq/L, patient receiving digoxin	Order for K <sup>+</sup> supplementation
Mg <sup>2+</sup> <1.8 mEq/L, patient receiving digoxin	Order for Mg <sup>2+</sup> supplementation
No recent Mg <sup>2+</sup> level, patient receiving digoxin	Order for an Mg <sup>2+</sup> level
No recent K <sup>+</sup> level, patient receiving digoxin	Order for a K <sup>+</sup> level
No recent digoxin level, patient receiving digoxin currently and in the past	Order for a digoxin level

K<sup>+</sup> = potassium; Mg<sup>2+</sup> = magnesium.

Characteristics of the control and study groups were compared using Student's t-test for continuous variables and the  $\chi^2$  statistic for proportions. A p-value of 0.05 was chosen for statistical significance of all comparisons.

### Results

During the study period, the CDS generated 775 alerts, whereas in the control period, 821 equivalent alerting situations were identified. Characteristics of the control and study groups are shown in Table 2. Both the control and study periods included 310 patients, many of whom had more than one alert or alerting situation. The average patient ages in the control and study groups were not statistically different, 61 (standard deviation = 16) years and 59 (standard deviation = 20) years, respectively ( $p = 0.31$ ). Gender representations in both groups were not statistically different. The average potassium or magnesium levels for the untreated hypokalemia or hypomagnesemia alerts were not statistically different between the control and study groups for either the synchronous or asynchronous alerts.

An independent manual critical laboratory reporting system is used for potassium levels <3.0 mEq/L. Thus, the CDS system may generate alerts duplicating the efforts of the existing reporting system when the potassium was <3.0 mEq/L. The proportions of alerts or alerting situations that also engaged the critical reporting system were not different in the control and study periods (13.5% vs. 12.9%, respectively,  $p = 0.99$ ). Because the critical reporting system was in place and fired with similar frequencies in the control and study periods, the critical reporting system was not considered in this analysis.

The synchronous CDS alerts were displayed to a variety of types of clinicians. Based on the first 115 generated alerts, the receiving clinicians were primarily housestaff physicians

Table 2 ■ Control and Study Group Characteristics

	Control Group	Study Group
Number of alerts or alerting situations		
Synchronous, no digoxin level	220	169
Synchronous, no K <sup>+</sup> level	35	37
Synchronous, no Mg <sup>2+</sup> level	209	223
Synchronous, low Mg <sup>2+</sup>	36	39
Synchronous, low K <sup>+</sup>	23	31
Asynchronous, low Mg <sup>2+</sup>	121	136
Asynchronous, low K <sup>+</sup>	177	140
Total	821	775
Electrolyte concentrations of alerts or alerting situations	Average (mmol/L)	Average (mmol/L)
Synchronous, low Mg <sup>2+</sup>	1.57 ± 0.19	1.62 ± 0.12 (NS)
Synchronous, low K <sup>+</sup>	3.17 ± 0.32	3.24 ± 0.18 (NS)
Asynchronous, low Mg <sup>2+</sup>	1.60 ± 0.16	1.60 ± 0.16 (NS)
Asynchronous, low K <sup>+</sup>	3.17 ± 0.33	3.20 ± 0.20 (NS)
Critical results for K <sup>+</sup> <3.0		
Asynchronous, low K <sup>+</sup>	24 (13.5%)	18 (12.9%) (NS)
Number of unique patients	310	310
Age (yr)	61 ± 16	59 ± 20 (NS)
% Female	48%	53% (NS)

± correspond to the standard deviation; NS designates no statistically significant difference between the values in the control and study groups.

(80%); the remainder were pharmacists (9%), nurses (5%), or medical students (5%) placing orders under the supervision of a physician. These data are consistent with those of the operations at our institution, where housestaff physicians place the majority of the orders.

Table 3 displays the control and study group response rates for each alert at one and 24 hours as well as the compliance curve comparisons. Digoxin and electrolyte concentrations were monitored more frequently after the CDS alerts were instituted than in the control period. Within one hour of ordering digoxin in the control period, only 9% of clinicians had ordered potassium levels and only 12% had ordered magnesium levels compared with 57% and 40%, respectively, after CDS implementation ( $p < 0.01$  for both). At 24 hours, less than half of the control patients had potassium (49%) or magnesium (44%) levels ordered compared with 81% and 66%, respectively, after implementing the CDS alerts ( $p < 0.01$  for both). Ordering of digoxin levels increased from 6% to 19% at one hour and 22% to 38% at 24 hours ( $p < 0.01$  for both). These results are represented as a function of time in Figure 1. The compliance curves for digoxin, magnesium, and potassium were all improved after alert implementation ( $p < 0.001$  for all).

Figure 2 shows the compliance curves for the synchronous alerts associated with untreated hypokalemia and hypomagnesemia. Overall clinician compliance, defined as potassium and/or magnesium supplementation, was not statistically improved by the alerts. However, as indicated in Table 3, the proportion of patients with magnesium supplementation at one hour was statistically improved after CDS alert intervention (6% vs. 23%,  $p < 0.05$ ), although not at 24 hours (47% vs. 56%,  $p = 0.57$ ).

Table 3 ■ Response Rates at 1 and 24 Hours

Alert or Alerting Situation	Compliance (1 hr)		Compliance (24 hr)		Comparison of Curves* (p-value)
	Control Group (%)	Study Group (%)	Control Group (%)	Study Group (%)	
Synchronous, no digoxin level	6	19†	22	38†	0.0003
Synchronous, no K <sup>+</sup> level	9	57†	49	81†	0.0001
Synchronous, no Mg <sup>2+</sup> level	12	40†	44	66†	0.0000
Synchronous, low Mg <sup>2+</sup>	6	23‡	47	56 (NS)	<0.2
Synchronous, low K <sup>+</sup>	22	39 (NS)	74	65 (NS)	<0.2
Asynchronous, low Mg <sup>2+</sup>	5	49†	70	87†	0.0000
Asynchronous, low K <sup>+</sup>	6	35†	77	93†	0.0000

NS designates no statistically significant difference between the values in the control and study groups.

K<sup>+</sup> = potassium; Mg<sup>2+</sup> = magnesium.

\*Comparisons of compliance curves made using log-rank statistic.

† $p < 0.01$  using  $\chi^2$  test.

‡ $p < 0.05$  using Fisher's exact test.

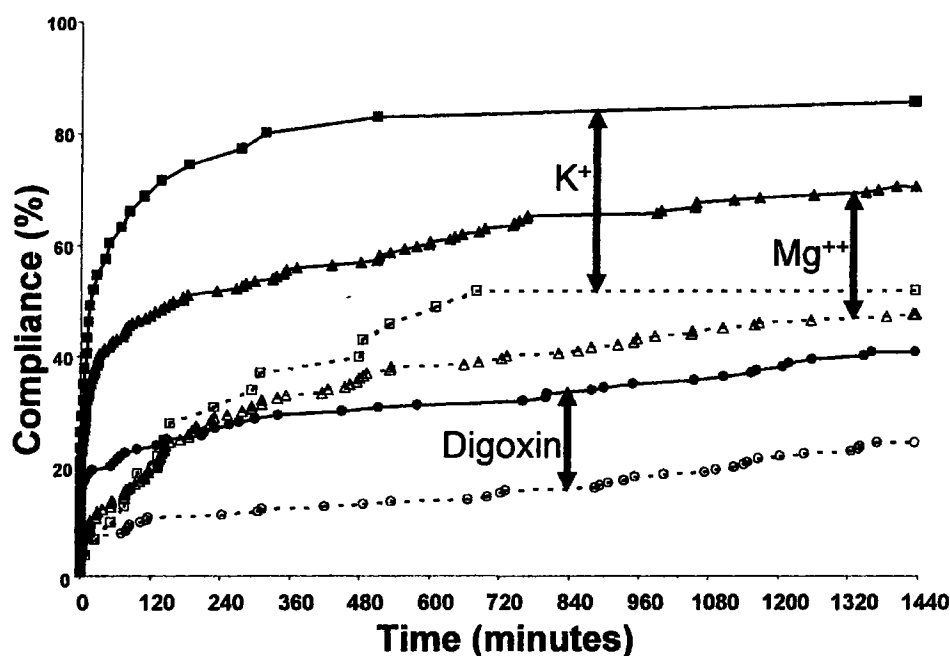
Figure 3 shows the compliance curves for the asynchronous alerts associated with newly reported hypokalemia and hypomagnesemia. Compliance was significantly greater in the CDS study group in both time periods. At one hour, both magnesium and potassium supplementation occurred more frequently in the CDS study group compared with the control group (49% vs. 5% for magnesium and 35% vs. 6% for potassium;  $p < 0.01$  for both). These differences remained significant at 24 hours (87% vs. 70% for magnesium and 93% vs. 77% for potassium;  $p < 0.01$  for both). The overall curves were also improved for magnesium and potassium ( $p < 0.0001$  for both).

## Discussion

This study evaluated the effectiveness of automated decision support alerts in changing clinician behavior in a CPOE environment. Certain alerts were displayed in real time, directly to the clinician, synchronous to the act of ordering digoxin. These synchronous alerts recommended internally developed appropriate guidelines of care for safe use of digoxin. Asynchronous alerts based on newly reported laboratory results were also generated. Statistical analysis clearly demonstrates that five of the CDS alerts increased the speed of clinician response to the clinical situation and enhanced overall clinician compliance at 24 hours. These results are consistent with the literature, with Rind et al.<sup>12</sup> finding a more rapid response to worsening renal dysfunction with asynchronous alerts. A study on synchronous corollary orders also demonstrated improved compliance with institutional practice guidelines for a variety of order types.<sup>13</sup>

Compliance curves for the control group represent the response of clinicians to the clinical situations prior to alert implementation. The control group curves for the five synchronous alerts (Figs. 1 and 2) indicate that at the time of ordering digoxin, only a limited number of clinicians placed orders appropriate to address the relevant clinical situation. This may be due to the fact that the clinician was not always aware of the clinical situation. Over the successive 24 hours, a more linear trend evolves as more clinicians took appropriate action. However, the curves for the study group demonstrate distinctly different clinician behavior after alert implementation. While ordering digoxin, the clinician was alerted to the clinical situation and was able to take immediate action in response to the alert. The curves for the study group clearly indicate a higher rate of initial compliance after alert generation, with the exception of untreated hypokalemia. It is not clear why the response to hypokalemia did not improve with the alerts.

The synchronous alerts associated with no recent levels of digoxin, magnesium, or potassium (Fig. 1) demonstrated improved clinician response and compliance; however, the magnitudes of the responses were not equal. It is interesting to note that clinicians ordered digoxin levels less frequently than potassium and magnesium levels both before and after alert implementation ( $p < 0.001$ ). In fact, clinician response to the CDS alerts indicating no digoxin level for the study group was actually no better than the clinician response to unknown potassium and magnesium levels in the control group before the CDS alerts were even employed. Clinically, digoxin concentrations are of limited use unless toxicity or medication



**Figure 1.** Compliance curves for unknown digoxin, potassium ( $K^+$ ), and magnesium ( $Mg^{2+}$ ) levels. Proportions of patients with orders checking digoxin ( $\circ$ ),  $K^+$  ( $\square$ ), and  $Mg^{2+}$  ( $\triangle$ ) levels after digoxin was ordered with no recent levels recorded. The x-axis represents time to clinician order for the laboratory level. Clinician response for the control group is represented by the open symbols ( $\circ$ ,  $\square$ ,  $\triangle$ ) and dashed lines, and the response for the study group is indicated by the solid symbols ( $\bullet$ ,  $\blacksquare$ ,  $\blacktriangle$ ) and solid lines. Responses for the study group were significantly improved for all three alerts ( $p < 0.001$  using the log-rank statistic). Arrows are included for easier identification of each pair of control/study curves.

noncompliance is suspected. Therefore, routine monitoring of digoxin levels may not always be appropriate and could explain the lower rate of clinician compliance with this recommendation.

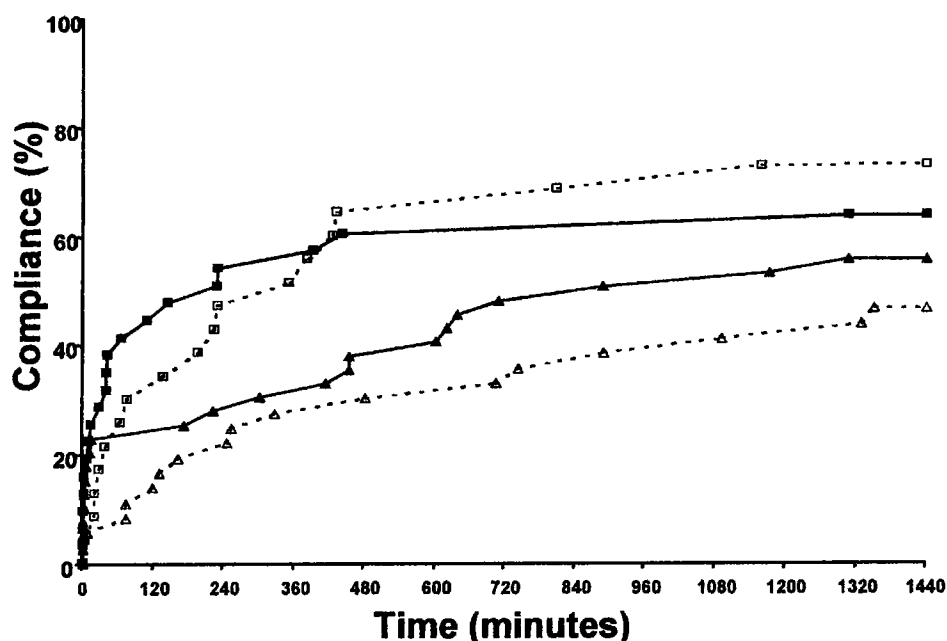
The control curves for the asynchronous alerting situations (Fig. 3) indicate a very limited initial response in the first hour, with gradual increases in compliance over time. Early response is probably related to the likelihood that a clinician will access the EMR and recognize the low electrolyte value. However, our data indicate that clinicians are more likely to treat electrolyte deficiencies and do so much more rapidly after alert implementation. CDS alerts for newly reported hypokalemia in patients being given digoxin have been previously studied, using an automatic paging system to deliver the alert to an appropriate clinician.<sup>20</sup> Unfortunately, the study did not provide specific analysis of this hypokalemia alerting system that can be compared with the findings of our study.

The clinician response to low electrolytes prior to alert implementation shows an interesting pattern. The responses to newly reported low magnesium or low potassium were roughly the same (70% vs. 77%,  $p = 0.2$ , at 24 hours; control curves in Fig. 3). At the time of ordering digoxin, however, the control responses to low levels of the two electrolytes were very different; there was a higher attentiveness to low potassium than to low magnesium (74% vs. 47%,  $p = 0.02$ ) after 24 hours (control curves in Fig. 2). It is interesting to speculate on the reason for this difference. While ordering a medication, a clinician needs to actively review the patient's clinical data. If the clinician does not realize that a certain

element of data is relevant, the information will not be considered when placing the order. In this case, the compliance curves indicate that clinicians were less aware of the importance of hypomagnesemia in digoxin use than the importance of hypokalemia. However, responding to a newly reported low electrolyte level does not necessarily require a full contextual clinical understanding but rather an appropriate reaction to the new result.

The above discussion emphasizes the importance of showing clinicians all relevant clinical information on the same visual interface used to order medications. It may have been possible to improve the supplementation of magnesium at the time of ordering digoxin by proactively displaying the low magnesium level to the clinician at the initial stages of the ordering process. This proactive approach may be preferred to the annoyance that may be experienced when clinicians are forced to respond to CDS-generated alerts. Users may prefer to be given the data that they need to make good decisions rather than to be criticized or asked to respond when they make poor decisions. Proactive decision support must be further studied to better understand the impact on physician practice patterns.

Analysis of the compliance curves associated with low magnesium or potassium demonstrates that asynchronous alerts were successful in changing clinician behavior, whereas the synchronous alerts generally were not. The reason for this discrepancy is not certain, but several hypotheses are plausible. When an alert reporting a new low electrolyte value is printed to the nursing station, it is verbally communicated by a nurse to the house officer. This resulting



**Figure 2.** Compliance curves for synchronous alerts. Proportion of patients with orders for electrolyte supplementation after digoxin was ordered with a low potassium ( $K^+$ ) ( $\square$ ) or magnesium ( $Mg^{2+}$ ) ( $\triangle$ ) levels. The x-axis represents time to clinician order for supplementation. Clinician response is indicated for the control groups with open symbols ( $\square$ ,  $\triangle$ ) and dotted lines and for the study group with solid symbols ( $\blacksquare$ ,  $\blacktriangle$ ) and solid lines. The respective control versus study group curves are not statistically different, but the supplementation of  $Mg^{2+}$  was higher at one hour using Fisher's exact test.

nurse-to-resident human interaction may be a more effective communication method than an alert window presented to the resident on the computer screen in CPOE. Implicit in this discussion is the culture of an academic teaching hospital. Houseofficers quickly learn to respond to nurse requests, whereas there are no immediate consequences of ignoring an on-screen computer-generated CDS alert. This discrepancy may also be related to the fact that nurses sometimes accept verbal orders for electrolyte supplementation, thus enabling easier compliance with the asynchronous alert recommendation. Thoughtful synchronous CDS alert design may be able to remedy the ease of alert recommendation compliance by enabling ordering directly from the alert window. By including easily initiated orders for supplementation directly in the alert interface, we may find that the compliance with the recommendations for electrolyte supplementation will improve.

Comparing the effectiveness of all the synchronous alerts also provides information regarding how the clinical content of the alert may influence its effectiveness. All the synchronous alerts interacted with the ordering clinician in a visibly identical manner, with a pop-up window of identical size and color and text of identical font and color. The only difference was the clinical content provided by the alert. Of the five synchronous alerts, three were found to be effective in changing behavior, one was minimally effective, and one was not effective at all. One can conclude that the clinical content of the alerts affects their effectiveness.

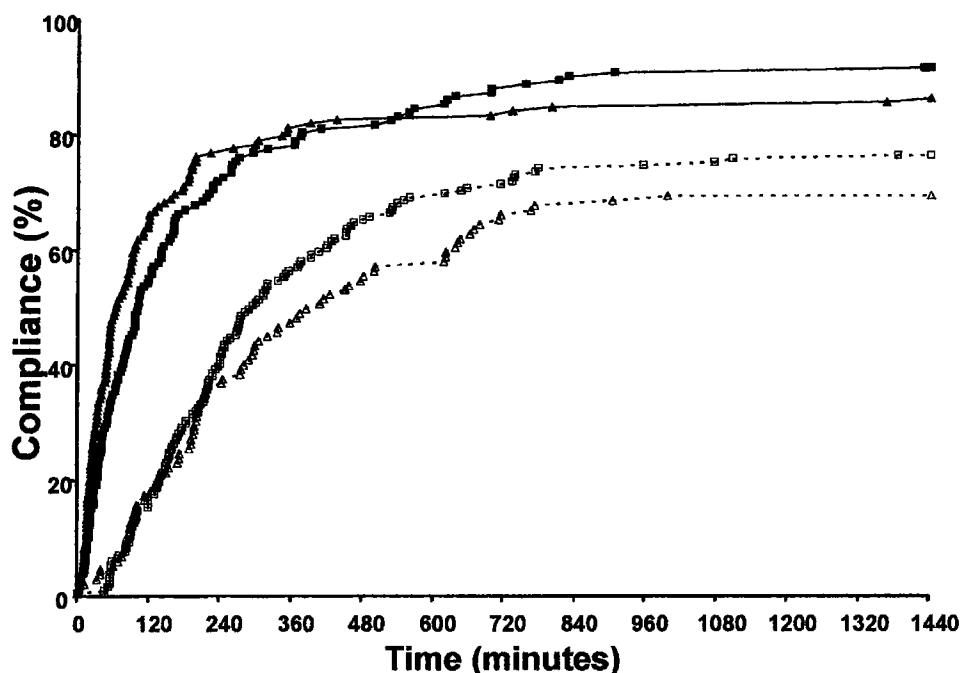
Although this finding may seem obvious, it is possible that clinicians may ignore the content of these pop-up windows because they have become desensitized to repeated alerts and grow accustomed to ignoring pop-up messages while browsing the Internet and using many different applications

that use them. Our data clearly demonstrate that these alerts were at least sometimes read and were efficacious, but obviously we cannot measure the effect of future desensitization, and studies at our institution and others need to address this important question.

The data presented here suggest that the CDS alerts improved both the speed and magnitude of clinician responses. This is clearly evidenced by the asynchronous alerts indicating a low potassium or low magnesium level for patients receiving digoxin. Collectively, a sevenfold improvement in the proportion of patients with an order for electrolyte supplementation was demonstrated at one hour. This dramatic improvement at one hour likely represents the ability for automation to speed up the presentation of the relevant information to clinicians. Laboratory alerts have been previously demonstrated as a means to reduce the time to result notification.<sup>12,20-22</sup> The 20%–25% improvement noted after 24 hours likely represents the ability of CDS alerts to educate clinicians of the relevance of the new information. By improving clinician response to potentially adverse clinical situations, medication errors and ADEs may be reduced, but more studies are necessary to confirm this hypothesis.

### Limitations

The control group was historical rather than concurrent and prospective. The hospital-wide implementation of CDS did not allow a prospective, randomized trial design. Because many houseofficers were associated with both the control and study groups and because no other quality improvement or educational programs were developed related to digoxin use, this limitation in study design is unlikely to mitigate the results.



**Figure 3.** Compliance curves for asynchronous alerts. Proportions of patients with orders for electrolyte supplementation after newly reported low potassium ( $K^+$ ) ( $\square$ ) or magnesium ( $Mg^{2+}$ ) ( $\triangle$ ) levels. The x-axis represents time to clinician order for supplementation. Clinician response is indicated for the control groups with *open symbols* ( $\square$ ,  $\triangle$ ) and *dotted lines* and for the study group with *solid symbols* ( $\blacksquare$ ,  $\blacktriangle$ ) and *solid lines*. Clinician response significantly improved in both situations with  $p < 0.0001$  using the log-rank statistic.

Another issue with the control group was that the two time periods were different compared with the academic schedule. New housestaff physicians typically begin in July and finish in June, implying they are more experienced clinicians in June than in July. If we count the days of the academic year starting in July, the control period would have an average of 204 days in the academic year and the trial period would be 177 days. Although we do not know a priori what the effect of training would be on clinical response to the situations studied, it is difficult to assume that a reduction in training of this slight amount is the cause of the improved measured response.

The study did not consider CDS alert effectiveness based on the clinician role. As additional studies concerning CDS are published, we may find the effect of alerts on clinician practice may be related to the type of clinician and the level of training (i.e., attending, housestaff, nurse).

Renal dysfunction is also a critical consideration in the safe use of digoxin.<sup>14,16</sup> CDS addressing renal function was not available and was therefore not examined in this study. We have since implemented CDS for renal dysfunction and are currently studying its effect on digoxin dosing.

Although we were able to show that the asynchronous alerts for electrolyte deficiency were effective and the synchronous alerts were not, the study was not designed to know for certain which aspect of the synchronous versus asynchronous mode of communication caused the difference. Because the verbiage, mode of communication, and activity of the clinicians at the time of the alerts varied slightly, we cannot state for certain which aspects of the alerts account for the differences noted here.

Last, our results do not comment on the clinical impact of CDS alerts. Although clinician compliance was improved by the alerts, we did not measure the impact this had on medication errors or ADEs related to digoxin use. As this technology evolves, outcome analyses must be performed to better assess the clinical utility of such systems.

## Conclusion

We developed and implemented CDS for the inpatient use of digoxin in a CPOE environment. Both synchronous CDS alerts generated in real time during CPOE and asynchronous alerts influenced clinician behavior. The alerts generally acted to improve both the speed and overall magnitude of appropriate clinician response to a clinical situation. We were able to measure the effectiveness of both synchronous and asynchronous alerts in a similar clinical scenario, namely, hypomagnesemia or hypokalemia in patients being given digoxin, and found that the asynchronous alerts were effective in promoting electrolyte supplementation, whereas the synchronous alerts were not. Thus, response to the alerts depended on both the manner in which the alert was communicated to the clinician, synchronous or asynchronous, and the clinical content of the alert.

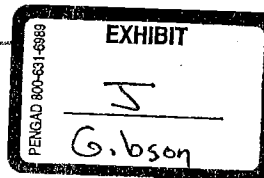
## References ■

1. Bates DW, Spell N, Cullen DJ, et al. The costs of adverse drug events in hospitalized patients. *JAMA*. 1997;277:307-11.
2. Classen DC, Pestotnik SL, Evans S, et al. Adverse drug events in hospitalized patients. *JAMA*. 1997;277:301-6.
3. Johnson JA, Bootman JL. Drug-related morbidity and mortality: a cost-of-illness model. *Arch Intern Med*. 1995;155:1949-56.

4. Bates DW, Boyle DL, Vander Vliet MD, et al. Relationship between medication errors and adverse drug events. *J Gen Intern Med.* 1995;10:199-205.
5. Bates DW, Cullen D, Laird N, et al. Incidence of adverse drug events and potential adverse drug events: implications for prevention. *JAMA.* 1995;274:29-34.
6. Bates DW, Leape LL, Petrycki S. Incidence and preventability of adverse drug events in hospitalized adults. *J Gen Intern Med.* 1993;8:289-94.
7. Leape LL, Lawthers AG, Brennan TA, Johnson WG. Preventing medical injury. *Qual Rev Bull.* 1993;19:144-9.
8. Kaushal R, Bates DW, Landrigan C, et al. Medication errors and adverse drug events in pediatric patients. *JAMA.* 2001;285:2114-20.
9. Bond CA, Raehl CL, Franke T. Medication errors in United States hospitals. *Pharmacotherapy.* 2001;21:1023-36.
10. Bates DW, Leape LL, Cullen DJ, et al. Effect of computerized physician order entry and a team intervention on prevention of serious medication errors. *JAMA.* 1998;280:1311-6.
11. Kaushal R, Shojania KG, Bates DW. Effects of computerized physician order entry and clinical decision support systems on medication safety: a systematic review. *Arch Intern Med.* 2003;163:1409-16.
12. Rind DM, Safran C, Phillips RS, et al. Effect of computer-based alerts on the treatment and outcomes of hospitalized patients. *Arch Intern Med.* 1994;154:1511-7.
13. Overhage JM, Tierney WM, Zhou XH, McDonald CJ. A randomized trial of "corollary orders" to prevent errors of omission. *J Am Med Inform Assoc.* 1997;4:364-75.
14. Kelly RA, Smith TW. Recognition and management of digitalis toxicity. *Am J Cardiol.* 1992;69:108G-19G.
15. Roberts SA, Diaz C, Nolan PE, et al. Effectiveness and costs of digoxin treatment for atrial fibrillation and flutter. *Am J Cardiol.* 1993;72:567-73.
16. Gandhi AJ, Vlasses PH, Morton DJ, Bauman JL. Economic impact of digoxin toxicity. *Pharmacoeconomics.* 1997;12:175-81.
17. Galanter WL, DiDomenico J, Polikaitis A. Preventing exacerbation of an ADE with automated decision support. *J Healthc Inf Manage.* 2002;16(4):44-9.
18. Raschke RA, Gollihare B, Wunderlich TA, et al. A computer alert system to prevent injury from adverse drug events. *JAMA.* 1998;280:1317-20.
19. Rind DM, Davis R, Safran C. Designing studies of computer-based alerts and reminders. *MD Comput.* 1995;12:122-6.
20. Kuperman GJ, Teich JM, Tanasijevic MJ, et al. Improving response to critical laboratory results with automation: results of a randomized controlled trial. *J Am Med Inform Assoc.* 1999;6:512-22.
21. Tate KE, Gardner RM, Weaver LK. A computerized laboratory alerting system. *MD Comput.* 1990;7:296-301.
22. Shabot MM, LoBue M, Leyerle BJ, Dubin SB. Decision support alerts for clinical laboratory and blood gas data. *Int J Clin Monit Comput.* 1990;7(1):27-31.

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# Mechanisms, Manifestations, and Management of Digoxin Toxicity in the Modern Era

Jerry L. Bauman,<sup>1,2</sup> Robert J. DiDomenico<sup>1,2</sup> and William L. Galanter<sup>3</sup>

1 Department of Pharmacy Practice, University of Illinois at Chicago, Chicago, Illinois, USA

2 Department of Medicine, Section of Cardiology, University of Illinois at Chicago, Chicago, Illinois, USA

3 Department of Medicine, Section of General Internal Medicine, University of Illinois at Chicago, Chicago, Illinois, USA

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## Abstract

Because of the common use of digoxin and because of its narrow therapeutic index, digoxin toxicity has been prevalent historically and, therefore, most clinicians are well aware of the classical dose/concentration-related signs and symptoms of toxicity. Yet, in the modern era the incidence of digoxin toxicity has been declining for a variety of reasons, including a new (lower) therapeutic range, the development of more effective drug therapies for heart failure, and more accurate dosing methods. In addition, digoxin toxicity, once commonly fatal, can now be quickly and effectively treated by the emergency administration of antidigoxin Fab fragments. Indeed, it may be possible to expand the use of Fab fragments to select patients with non life-threatening digoxin toxicity, in order to save costs and improve patient comfort. Most cases of digoxin toxicity are caused by inappropriately high dosages, which are usually prescribed in the setting of renal dysfunction, while other cases can be attributed to system errors such as multiple prescriptions, poor patient counseling, or errors in transcribing. With modern computerized prescribing systems, such as direct physician order entry and prompts that alert the clinician to the potential for error, it is possible to decrease the incidence of digoxin toxicity even further. A realistic goal is to nearly eradicate once commonplace digoxin toxicity or at least make its occurrence a rare event.

Throughout its more than 230 years of clinical use, the picture of digoxin toxicity has continued to evolve.

Early in its clinical use, it was relatively common to employ a strategy of escalating the dose of digoxin until adverse effects were observed. Indeed, this antiquated practice resulted in a clear clinical description of the various manifestations of digoxin toxicity, which are now well known to most clinicians.

Subsequent important clinical advances, however, led to a decline in the frequency of digoxin toxicity. Firstly, routine clinical serum digoxin concentrations became available, with the

resulting acceptance of a therapeutic range.<sup>[1-3]</sup> Secondly, pharmacokinetic methods were utilized to develop dosing guidelines designed to achieve digoxin concentrations within the therapeutic window.<sup>[4,5]</sup> Simultaneously, for those unfortunate patients who experienced life-threatening digoxin toxicity, the creation, approval, and subsequent commercial availability of the Fab portion of digoxin antibodies proved to be much more effective than other treatments. Simply put, lives have been saved because of the administration of anti-digoxin Fab fragments. Most recently, the results of the DIG (Digitalis Investigative Group) trial,<sup>[6]</sup> published

in 1997, were crucial in clarifying the place of digoxin in the treatment of heart failure relative to other therapies such as  $\beta$ -adrenoceptor antagonists and angiotensin II type 1 antagonists. *Post-hoc* analyses of the DIG trial have helped further refine the clinical use of digoxin, including its therapeutic range.<sup>[7,8]</sup>

Thus, the evolution of knowledge regarding the clinical use of digoxin has resulted in a declining frequency and a different pattern and profile of digoxin toxicity. Nevertheless, patients still experience concentration-related digoxin toxicity as a result of dosing errors. The purpose of this article, therefore, is to review the clinical problem of digoxin toxicity in the modern era.

## 1. Pharmacology

An understanding of the complex pharmacological actions of digoxin will help to explain its toxic manifestations.<sup>[9-12]</sup>

Digoxin is a weak positive inotrope that indirectly increases calcium availability to the contractile elements of the myofibril by inhibiting  $\text{Na}^+\text{-K}^+$  ATPase.<sup>[13,14]</sup> Inhibition of this ATPase results in an increase in intracellular  $\text{Na}^+$  which, in turn, causes the  $\text{Na}^+\text{-Ca}^{2+}$  exchanger to increase intracellular  $\text{Ca}^{2+}$ . At high/toxic digoxin concentrations, the storage capacity of the sarcoplasmic reticulum for  $\text{Ca}^{2+}$  becomes saturated, causing spontaneous release and reuptake of  $\text{Ca}^{2+}$ .  $\text{Ca}^{2+}$  overload coupled with the  $\text{Na}^+\text{-Ca}^{2+}$  exchanger, cause the inward movement of  $\text{Ca}^{2+}$  and  $\text{Na}^+$  during diastole that results in small electrical depolarizations termed afterdepolarizations.<sup>[15,16]</sup> These oscillations can summate, reach threshold, and cause rapid repetitive electrical impulses and/or trigger re-entry. The afterdepolarizations triggered indirectly by excess  $\text{Ca}^{2+}$  (i.e. they are an extension of the positive inotropic action of digoxin) more than likely underlie the primary mechanism for most digoxin-induced tachycardias.<sup>[17,18]</sup>

The effects of digoxin on the autonomic nervous system have also been well described.<sup>[9-11]</sup> Digoxin has parasympathomimetic actions that clinically manifest by increasing vagal tone to the sinus and atrioventricular (AV) nodes, thus decreasing HR and slowing conduction through the AV node. In patients with heart failure, digoxin has anti-sympathetic effects, including restoration of baroreceptor sensitivity (which is decreased in low-output heart failure).<sup>[19-21]</sup> The exact underlying mechanism for these effects remains unclear but the sympatholytic actions first appear at relatively low digoxin concentrations – below those needed to cause a measurable increase in the force of contraction. In heart failure, low concentrations of digoxin decrease serum norepinephrine (and other neurohormonal) levels.<sup>[22]</sup> Indeed, many authors now feel that the therapeutic effects of digoxin (such as those noted in the DIG trial) in patients with heart failure can be predominantly attributed to its action as a sympatholytic, blocking

compensatory neurohormones (not unlike  $\beta$ -adrenoceptor antagonists) rather than its well known inotropic effects.<sup>[14,21,22]</sup>

Digoxin is a substrate for p-glycoprotein, a membrane transport pump that is present not only in the intestine but also in many other organs such as the CNS and the kidney. P-glycoprotein modulates the oral absorption of digoxin, in addition to its renal excretion and movement across the blood-brain barrier.<sup>[23]</sup> The oral bioavailability of digoxin ranges from 70% to 90%.<sup>[24]</sup> The mechanism for well described drug interactions with digoxin can, in many cases (e.g. verapamil, quinidine, and amiodarone), be attributed to the inhibition of p-glycoprotein.<sup>[25,26]</sup> By inhibiting p-glycoprotein, these agents increase serum digoxin concentrations by increasing its intestinal absorption and decreasing renal clearance.

The elimination half-life ( $t_{1/2}$ ) of digoxin in patients with normal renal function is about 1.6 days but can be 4–6 days in patients with end-stage renal dysfunction and, therefore, without appropriate intervention, toxic effects can persist for several days to weeks.<sup>[24]</sup> Digoxin has a relatively large volume of distribution (5–7 L/kg) and is highly tissue bound, making dialysis ineffective in the treatment of toxicity.<sup>[24]</sup>

The accepted therapeutic range for digoxin has changed in the past few years. Historically, the window was 1.0–2.5 nmol/L (0.8–2.0  $\mu\text{g/L}$ ), with toxicity more common above concentrations of 2.5 nmol/L.<sup>[1,2]</sup> While the upper border of this range still has useful value in aiding the diagnosis of digoxin toxicity, concentrations between 0.6 and 1.2 nmol/L (0.5–1.0  $\mu\text{g/L}$ ) [i.e. about half of the concentrations felt to be desirable in the past] should now be targeted in patients with heart failure. The data supporting this new range come from *post-hoc* analyses of major multicenter clinical trials. Initially, Adams et al.<sup>[7]</sup> analyzed data from two large digoxin 'withdrawal' studies. In general, patients with low serum concentration of digoxin (0.6–1.1 nmol/L [0.5–0.9  $\mu\text{g/L}$ ]) fared better, including having statistically fewer episodes of heart failure exacerbation, compared with those receiving placebo. Consistent with these data was the *post-hoc* analysis of the DIG trial (figure 1).<sup>[8]</sup> In that analysis, low digoxin concentrations (0.6–1.0 nmol/L or 0.5–0.8  $\mu\text{g/L}$ ) were associated with better clinical outcomes and lower mortality. In contrast, digoxin concentrations >1.5 nmol/L (1.2  $\mu\text{g/L}$ ) were associated with higher mortality rates and a greater incidence of digoxin toxicity. Although the authors attempted to control the confounding factors that may have influenced mortality and digoxin levels (e.g. concurrent renal dysfunction), cause and effect were difficult to definitively ascertain. Nonetheless, these findings have fueled a clinical trend to use lower dosages of digoxin (0.125 mg/day vs 0.25 mg/day) in most patients with heart failure; this should result in lower rates of digoxin toxicity.

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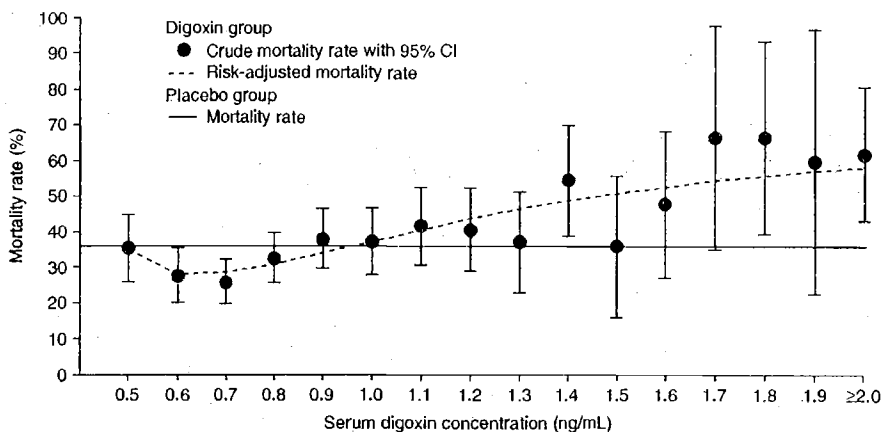


Fig. 1. Relationship between serum digoxin concentration and all-cause mortality in a *post-hoc* analysis of the DIG (Digitalis Investigative Group) trial (reproduced from Rathore et al.,<sup>[6]</sup> with permission). Note the statistically significant decrease in mortality (compared with placebo) at digoxin concentrations of 0.6–0.7 ng/mL ( $\mu\text{g/L}$ ) and the trend toward increasing mortality at concentrations  $>1.0$  ng/mL. These data have helped to redefine the therapeutic range of digoxin to a lower window of concentrations and may be expected to contribute to a further decline in the incidence of toxicity.

## 2. Incidence and Causes

It is useful to compare previous estimates of digoxin toxicity with more recent data. For instance, in a classic paper in 1971 by Beller et al.,<sup>[2]</sup> nearly 25% of all patients treated with digoxin were classified as having “definite toxicity” and an additional 6% were felt to have signs or symptoms of “possible” digoxin toxicity. Importantly,  $>40\%$  of the patients with definite digoxin toxicity died. Data from the 1980s and the 1990s put the incidence of digoxin toxicity at about 4–5% in patients receiving digoxin.<sup>[27-29]</sup> In the DIG trial,<sup>[6]</sup> digoxin toxicity was diagnosed in 11.9% of patients receiving digoxin and in 7.9% of those receiving placebo; underscoring the sometimes difficult job of diagnosing digoxin toxicity. If one presumes that the incidence of falsely diagnosed digoxin toxicity was 7.9% (the incidence of digoxin toxicity in the placebo group), then the actual incidence of digoxin toxicity in the DIG trial was again about 4%.<sup>[6,30]</sup> In 1996, we analyzed the database of a large consortium of academic medical centers in the US and found that digoxin toxicity occurred in  $<0.1\%$  of all hospital admissions (836 cases in 1 189 839 admissions).<sup>[31]</sup> This demonstrates a relatively impressive decline over several decades in the magnitude of digoxin toxicity as a medical problem and correlates well with the now widespread use of serum concentration monitoring, improved dose-determination methods and awareness of drug interactions.

Why do patients still experience toxicity from digoxin? Aside from purposeful overdoses or suicide gestures, one can assume that digoxin toxicity occurs because of some medical error made by either the clinician or the patient and, thus, that most of these cases are preventable. Clearly one of the most important risks is

the presence of renal dysfunction: in one series,<sup>[32]</sup> two-thirds of patients with digoxin toxicity had moderate-to-severe renal disease (creatinine clearance  $<50$  mL/min for women or  $<60$  mL/min for men). We analyzed a series of 17 patients (16 with definite digoxin toxicity), in part, to gain an insight to this question.<sup>[31]</sup> Of the 16 patients, six (37.5%) experienced toxicity due to worsening renal function without a subsequent decrease in the dose of digoxin, another four patients (25%) experienced toxicity because the initial dose was too high for the patient (according to their renal function), and in one patient the dose was not decreased when amiodarone was added. Therefore, most patients experienced digoxin toxicity simply because they received a dosage that was too high (i.e. their dosage was not appropriately individualized). Four more patients (25%) experienced toxicity because, although they were prescribed an appropriate dosage, they self-administered digoxin inappropriately. For example, two patients received prescriptions for both 0.25 and 0.125 mg/day and the other two patients mistakenly took 0.25mg every day instead of every other day. Simple patient counseling and proper follow up could have prevented all four of these episodes of digoxin toxicity. The last patient received an appropriate dosage but the ultimate cause of digoxin toxicity could not be determined. Hence, nearly all of the cases reviewed (in this albeit small series) could have been prevented; some were clinician errors in judgment (e.g. wrong dosage) and some were ‘system’ errors (e.g. multiple prescriptions or lack of proper counseling). Regardless, it may be possible to put into place safeguards such as pharmacy computer systems with prompts and precautions that could decrease the incidence of digoxin toxicity even further (see section 5).

### 3. Manifestations

The signs, symptoms, and manifestations of digoxin toxicity have been well documented over the years.<sup>[9,12,16]</sup> They are traditionally divided into extra-cardiac and cardiac manifestations and although nearly every form of toxicity has been attributed to digoxin, a number are highly associated with true toxicity. Although unusual, digoxin toxicity has been reported to result in curious visual disturbances such as flashing lights, halos, and color disturbances (green-yellow patterns). More commonly, patients simply complain of hazy or blurred vision. Likewise, hallucinations have been reported but more common is the non-specific complaint of acute fatigue. Anorexia and nausea are extremely common; vomiting is less likely but not uncommon. These gastrointestinal symptoms occur in 30–70% of patients with reported digoxin toxicity.<sup>[6,28,29]</sup> Lacking the relatively unusual adverse effects that are somewhat pathognomonic for digoxin toxicity, often symptoms are nonspecific (e.g. nausea, blurred vision, and/or fatigue) and, therefore, the diagnosis of digoxin toxicity based solely on extra-cardiac symptoms can be difficult. Indeed in several recent large series of digoxin toxicity,<sup>[28,29,33]</sup> nausea/vomiting, anorexia, and fatigue are consistently the most frequently observed extra-cardiac symptoms.

One sign of serious digoxin toxicity that clinicians should always specifically target is hyperkalemia (i.e. serum potassium concentration  $>5.0$  mEq/L [ $>5.0$  mmol/L]). Hyperkalemia results from digoxin blocking  $\text{Na}^+\text{-K}^+$  ATPase diffusely throughout the body and the resultant leak of potassium from its intracellular home into extracellular spaces. Measurable hyperkalemia generally indicates extremely high concentrations of digoxin, often in the setting of renal dysfunction and traditionally prompts emergency treatment measures.

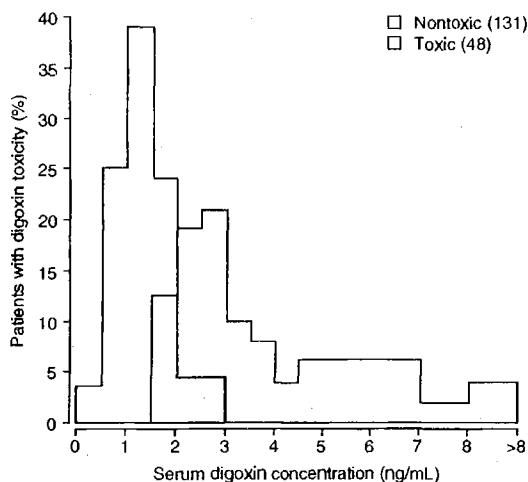
Digoxin has also been reported to cause nearly every rhythm disturbance; several are nearly diagnostic of digoxin toxicity and a number are rarely, if ever, due to digoxin.<sup>[12,16,34]</sup> Those that should be considered as digoxin-toxic rhythms unless proven otherwise (of course, in patients receiving digoxin) are new-onset Mobitz type I AV block (Wenckebach periodicity), accelerated junctional rhythm with or without high-degree AV block, non-paroxysmal atrial tachycardia with AV block, and bidirectional ventricular tachycardia. In patients with established atrial fibrillation, the regularization of ventricular rhythm represents complete heart block with an accelerated junctional escape due to digoxin toxicity. But analogous to the extra-cardiac signs and symptoms of digoxin toxicity, in many cases digoxin-induced arrhythmias are often nonspecific and may not necessarily alert the clinician to the toxic state. These include sinus bradycardia, premature ventricular complexes (PVCs) [e.g. bigeminy], and nonsustained ventricular

tachycardia. To gain an appreciation of the relative frequency of these rhythm disturbances, one could analyze multicenter studies that use digoxin antibody Fab fragments.<sup>[32,35]</sup> In the final report of one prospective trial,<sup>[35]</sup> it was reported that patients had experienced third-degree heart block (53%), sustained ventricular tachycardia (46%), ventricular fibrillation (33%), and asystole (11%). However, one criterion for entry into this trial was that patients had life-threatening arrhythmias. In other reports that included patients with non life-threatening digoxin toxicity, less serious rhythm disturbances (e.g. Mobitz type I second degree AV block, junctional rhythm, sinus bradycardia, or PVCs) were most common.<sup>[28,33]</sup> PVCs and digoxin-related tachycardias have historically been noted to be exacerbated by electrolyte disorders such as hypokalemia, hypomagnesemia, and hypercalcemia. Clinicians should also be aware of rhythm disturbances that are usually not attributable to digoxin toxicity. These include any supraventricular tachycardia with a rapid ventricular response and Mobitz type II AV block (the site of the block is usually below the AV node, unlike Mobitz type I block which is usually within the AV node).

Some authors have attempted to differentiate the signs and symptoms of toxicity based upon acute (e.g. purposeful or inadvertent overdose) or long-term (i.e. those with heart failure who are prescribed a maintenance dosage of digoxin that is too high) use.<sup>[36,37]</sup> However, these differences may simply be because of the magnitude of digoxin exposure. That is, patients who have ingested a large quantity of digoxin in a suicide attempt are more likely to display hyperkalemia and serious ventricular arrhythmias than those who have been prescribed a maintenance dosage that is too high (e.g. 0.25 mg/day instead of 0.125 mg/day). Regardless, as one can appreciate, it is sometimes difficult to diagnose digoxin toxicity because many of the more common signs or symptoms are relatively nonspecific (e.g. anorexia, PVCs) and could be due to other disorders. It is here that the determination of digoxin concentration is very useful. Although there is some overlap in 'therapeutic' and toxic levels, toxic symptoms are clearly more common above 2.5 nmol/L (2.0  $\mu\text{g/L}$ ) [figure 2].

### 4. Treatment of Digoxin Toxicity

Since the serious manifestations of digoxin toxicity are new-onset rhythm disturbances, traditional therapy has focused on these disorders. In patients with high-degree symptomatic AV block, intravenous atropine and temporary pacing have been recommended.<sup>[9-12]</sup> In patients with symptomatic ventricular arrhythmias, intravenous lidocaine and phenytoin have been recommended as the treatments of choice.<sup>[9-12]</sup> However, we can see little reason to recommend these therapies any longer because of the creation and commercial availability of digoxin antibody Fab



**Fig. 2.** Relationship between serum digoxin concentration and the diagnosis of digoxin toxicity in 179 patients from Dr Thomas Smith's original analysis in 1970 (reproduced from Smith et al.<sup>[1]</sup> with permission). Although there is some overlap between toxic and non-toxic concentrations, the value of determining a digoxin level to aid in the diagnosis of digoxin appears clear: 87% of the patients with digoxin toxicity have concentrations >2.0 ng/mL ( $\mu\text{g/L}$ ).

fragments. Concurrent therapies with agents such as activated charcoal, colestyramine, or colestipol have also been recommended in an attempt to bind digoxin in the gut.<sup>[38-40]</sup> These facilitate gastrointestinal elimination but also increase the systemic clearance of digoxin. Through both passive diffusion and perhaps enterohepatic recycling of digoxin, the intestine acts as a sink or dialysis membrane, with the binding resin or charcoal aiding in the elimination of digoxin. It appears as if activated charcoal is superior to binding resins such as colestyramine in patients who are likely to have significant quantities of digoxin present in the intestine, such as after a purposeful overdose.<sup>[41]</sup> However, it remains unclear which type of therapy (resins vs charcoal) is preferred in patients experiencing digoxin toxicity in the post-absorptive state. These therapies may play a role, predominantly in patients with non life-threatening signs or symptoms and concurrent renal dysfunction, where digoxin elimination would ordinarily take very long periods of time.

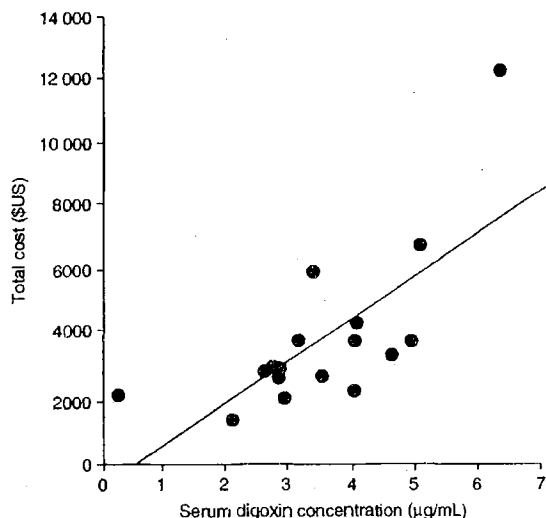
The use of Fab portions of antidigoxin antibodies prepared from sheep antiserum to reverse digoxin toxicity in humans was first reported in 1976.<sup>[42]</sup> In comparison to complete IgG antidigoxin antibodies, the use of just the Fab portion (cleaved from the Fc portion by papain) has the advantages of: (i) lower immunogenicity and incidence of allergic reactions; (ii) increased distribution to extravascular tissue sites; and (iii) increased systemic clearance by glomerular filtration and renal elimination.<sup>[43]</sup> Digoxin has a higher affinity for binding to the antidigoxin Fab fragment than to its physiologic receptor responsible for toxic signs and

symptoms. Therefore, the Fab fragments rapidly bind digoxin in the blood and interstitial fluid, causing a redistribution from intracellular tissue stores to the central compartment. Thus, despite the large volume of distribution of digoxin, the onset of action of antidigoxin Fab fragments in reversing digoxin toxicity is rapid (minutes). The volume of distribution of antidigoxin Fab is 0.4 L/kg and  $t_{1/2}$  is about 12–20 hours in patients with normal renal function ( $t_{1/2}$  is increased 10-fold in patients with severe renal dysfunction).<sup>[43]</sup> Although generally well tolerated, there are a number of adverse effects and complications of therapy to consider.<sup>[16,32,43]</sup> Minor allergic reactions may occur, although, to our knowledge, anaphylaxis has not been reported. Since digoxin will be immediately neutralized (and the activity of  $\text{Na}^+\text{-K}^+$  ATPase restored), exacerbation of heart failure (in left ventricular dysfunction), accelerated ventricular response (in atrial fibrillation), and hypokalemia may be observed. In the final report of a multicenter trial of patients with life-threatening digoxin toxicity, the rapid development of hypokalemia was documented in 4% of patients after the administration of antidigoxin Fab fragments.<sup>[35]</sup> Recrudescence of digoxin toxicity after an initial response to antidigoxin Fab has been reported in about 3% of patients in large multicenter trials.<sup>[32]</sup> Although there is no clear evidence that the stability of the Fab-digoxin complex wanes with time (releasing free digoxin), it is possible that the administration of inadequate amounts of Fab could result in a rebound increase in free digoxin concentrations caused by shifts in tissue stores. In a large post-marketing surveillance study,<sup>[32]</sup> it was discovered that the risk of recrudescence of digoxin toxicity was six times more likely if patients were given less than half of the calculated full neutralizing dose. It should also be noted that, from a practical viewpoint, serum digoxin concentrations cannot be usefully monitored after the administration of Fab fragments. Digoxin concentrations rise rapidly (as much as 30-fold) as the Fab fragment pulls digoxin from extravascular tissue stores into the plasma but these concentrations reflect the levels of the Fab-digoxin complex, not free unbound digoxin (which is negligible).

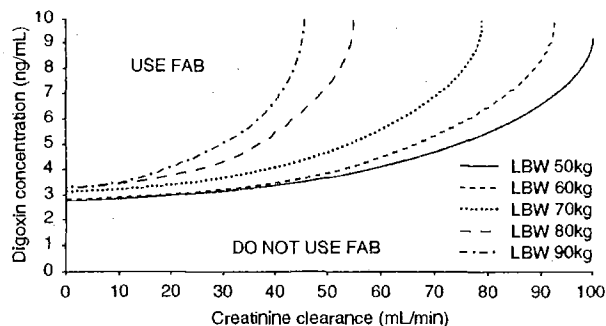
The administration of antidigoxin Fab to patients with digoxin toxicity is remarkably effective. In large multicenter trials, antidigoxin Fab has been shown to be 80–90% effective in rapidly and completely reversing all signs and symptoms of digoxin toxicity.<sup>[32,35]</sup> In most patients, the complete reversal of toxicity occurred within 4 hours.<sup>[35]</sup> The major reasons for lack of effectiveness were inadequate dosing and incorrect diagnosis. It is our opinion that antidigoxin Fab was used aggressively and perhaps sometimes inappropriately when it first became commercially available in 1986. However, antidigoxin Fab is expensive and these two issues (initial over-zealous use and high cost) have led to its subsequent, more limited, utilization in only those patients with

life-threatening arrhythmias or hyperkalemia. For instance, in more recent series of digoxin toxicity (including life-threatening and non-life-threatening presentations), antidigoxin Fab was only used in 4–6% of patients with this diagnosis.<sup>[29,31]</sup>

While it is clear that antidigoxin Fab should be administered to anyone with severe symptoms of digoxin toxicity, we think its use should be liberalized to include some patients with non life-threatening toxicity. In a burden-of-illness analysis, we found that hospitalization (bed) costs accounted for 93% of the total costs of digoxin toxicity.<sup>[31]</sup> In those patients with non life-threatening toxicity, the usual clinical scenario is that the patient is admitted for close observation only (without an intervention specifically targeted for digoxin toxicity) and is discharged after the signs and symptoms have resolved and the digoxin level has dropped below 2 µg/L. Indeed, the cost of digoxin toxicity correlated linearly with the digoxin concentration at the time of admission (figure 3). As a result of these data, we performed a cost-effectiveness analysis of antidigoxin Fab administration for use in patients with non life-threatening toxicity.<sup>[44]</sup> A nomogram was constructed that may aid clinicians in the decision whether to use or not use antidigoxin Fab for these patients (figure 4). In general, patients with higher digoxin serum concentrations (e.g. >3.6 nmol/L [3.0 µg/L]) and poorer renal function (e.g. creatinine clearance <50 mL/min) could receive antidigoxin Fab to reduce the length of stay and overall costs.



**Fig. 3.** Relationship between total cost (1995 values) of an episode of digoxin toxicity and digoxin concentration at admission in 17 patients<sup>[31]</sup> ( $r = 0.73$ ;  $p < 0.01$ ) [the one patient with a low digoxin concentration was diagnosed in error]. Patients are generally observed until the digoxin concentration drops below 2 µg/L and symptoms resolve.



**Fig. 4.** Nomogram for the clinical use of antidigoxin Fab (FAB) in patients with non-life threatening digoxin toxicity based upon a pharmacoeconomic analysis. The decision to use FAB or not is based upon the digoxin concentration, renal function (creatinine clearance), and lean body weight (LBW). For intersects above each line for LBW, the use of FAB will reduce overall cost of care (and improve patient symptoms); the use of FAB is cost effective. For patients who fall below each line, the cost of care with use of FAB is increased and therefore, FAB should not be used for economic reasons (reproduced from DiDomenico et al.,<sup>[44]</sup> with permission).

There are two commercial preparations of antidigoxin Fab available in the US (DIGIBIND® and DigiFab™)<sup>1</sup> and both are dosed in the same manner. In the case of an acute ingestion (e.g. overdose) where the amount ingested is known, one may estimate the quantity of antidigoxin Fab by equation 1:

$$\text{Dose (no. of vials)} = \frac{\text{Total amount ingested (mg)}}{0.5^*}$$

\* = mg of digoxin bound per vial of Fab

Alternatively, the estimation of the antidigoxin Fab dose can be completed by using a serum digoxin concentration in the following manner (equation 2):

$$\text{Dose (no. of vials)} = \frac{\text{Serum digoxin concentration (µg/L)} \times \text{weight (kg)}}{100}$$

To estimate the dose of anti-digoxin fab in milligrams (instead of vials), DIGIBIND® contains 38 mg/vial and DigiFab™ contains 40 mg/vial.

For the latter equation, the concentration used should be after the distribution from the central (blood) to the tissue compartment (i.e. at least 6 hours after the last dose). If the concentration is measured within this 6-hour window (during the distributive phase) the dose of antidigoxin Fab will be overestimated. If a distributive phase concentration is the only one available, using less than the full neutralizing dose (e.g. 50%) and observing for the resolution of symptoms has been suggested.<sup>[45]</sup> However, we recommend giving the full calculated dose if the patient has life-threatening symptoms: there is little harm (except excessive cost)

<sup>1</sup> The use of trade names is for product identification purposes only and does not imply endorsement.

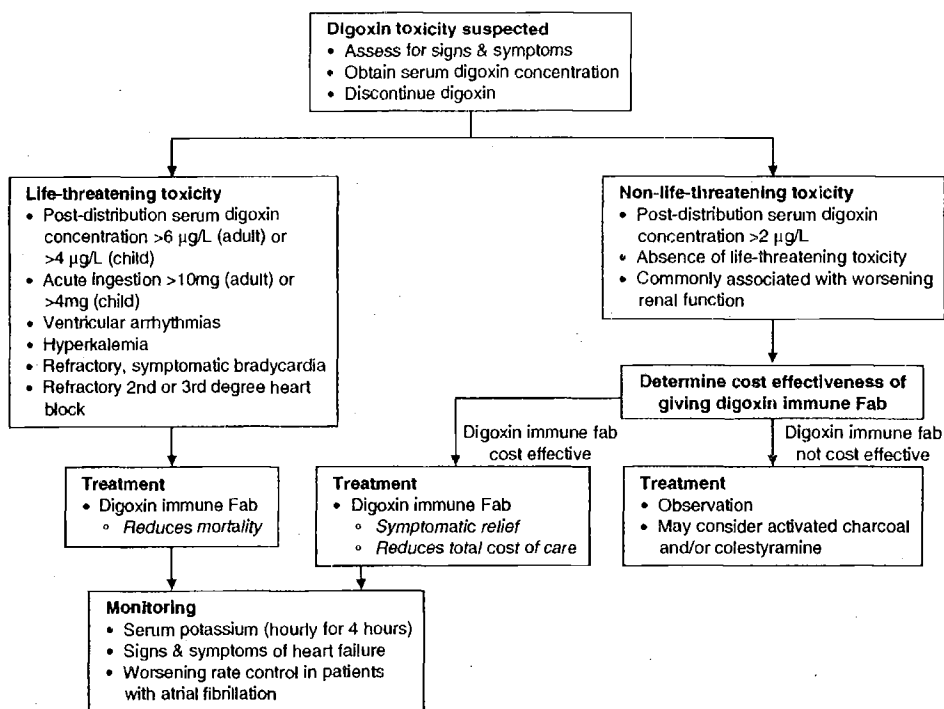


Fig. 5. Suggested algorithm for the clinical approach to digoxin toxicity.

of giving 'too much' Fab and this strategy minimizes the risk of recrudescence digoxin toxicity. Further, the strategy of giving less than the full estimated dose of Fab has not been systematically evaluated in large clinical trials.

In summary, the approach to digoxin toxicity can be summarized by grouping the patient's initial presentation into one of two categories (figure 5): (i) life-threatening toxicity (i.e. those with ventricular tachycardia, ventricular fibrillation, symptomatic high-degree AV block, sinus arrest, and/or hyperkalemia); and (ii) non life-threatening but symptomatic toxicity. In those patients with serious forms of toxicity, antidigoxin Fab fragments are administered for therapeutic reasons (to save a life and reverse serious symptoms), whereas in those with less serious presentations it may be administered on the basis of reducing the costs of care (by abbreviating hospital stay) and improving patient comfort. In patients with excess digoxin but with only very mild or no symptoms of digoxin toxicity, a conservative approach is recommended. One may consider binding resins or activated charcoal in order to enhance digoxin elimination (particularly in patients with renal dysfunction).

## 5. Prevention

Obviously, it is preferable to prevent digoxin toxicity rather than treat it. Adverse drug events, including digoxin toxicity, often result from errors in drug ordering, transcribing, dispensing, ad-

ministering, or monitoring.<sup>[46]</sup> It has been estimated that 20–69% of all adverse drug events may be preventable.<sup>[47–50]</sup> Likewise, given that most episodes of digoxin toxicity result from the failure to adjust the dosage in the presence of renal insufficiency or notable drug interactions,<sup>[31]</sup> it appears that most cases of digoxin toxicity could be avoided. There are some simple dose-determining guidelines that clinicians can use to prevent possible digoxin toxicity. For instance, one should initiate only 50% (e.g. 0.125 mg/day instead of 0.25 mg/day) of the dosage as estimated by Jelliffe's method<sup>[51]</sup> since this equation/nomogram was originally designed to achieve a steady-state digoxin concentration of 1.4 µg/L. Further, when adding agents known to interact with digoxin, such as amiodarone, the maintenance dosage of digoxin should be empirically cut in half (e.g. from 0.125 mg/day to 0.125mg every other day).

As computer technology continues to be integrated into the practices of medicine and pharmacy, embracing these technological advances may provide opportunities to prevent digoxin toxicity. As an important example, computerized physician order entry (CPOE) is being adopted at many healthcare facilities. Many of these CPOE systems utilize automated clinical decision support (CDS) technology, such as drug-allergy and drug-drug interaction checking. Several studies have shown that the use of these basic technologies reduces the incidence of adverse drug events.<sup>[51–54]</sup> The use of more sophisticated CDS systems has also been shown

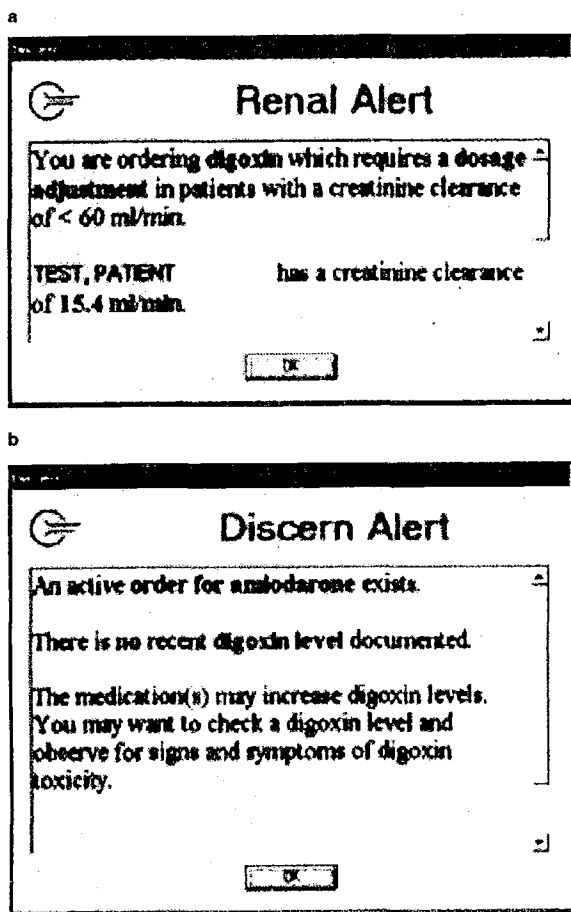


Fig. 6. Synchronous clinical decision support alerts for digoxin. Example of alerts that appear in real-time to digoxin-ordering clinician. Panel A alerts the ordering physician to the patient's renal insufficiency, suggesting dosage adjustment. Panel B alerts the clinician that the patient is also taking amiodarone, which may raise digoxin levels. Alerts also appear to the clinician ordering digoxin when electrolyte deficiencies are present that may increase the risk of digoxin toxicity (e.g. hypokalemia, hypomagnesemia).

to decrease adverse drug events related to anti-infective drugs<sup>[55]</sup> and to improve renal dosing of drugs.<sup>[56,57]</sup>

Because the risk of digoxin toxicity can be assessed using objective information readily available in a patient's chart, such as renal function, electrolyte levels, concomitant drug therapy, and serum digoxin concentration, it is an ideal target for the application of advanced CDS systems. We have developed such a system at the University of Illinois Medical Center.<sup>[58,59]</sup> The automated CDS rules for digoxin utilize patient-specific information recorded in the patient's electronic medical record, including serum electrolyte levels, estimated creatinine clearance, serum digoxin levels, and active orders for interacting drugs (e.g. amiodarone). When a clinician attempts to order digoxin (or an interacting drug in a

patient already taking digoxin), the automated CDS system screens the patient's electronic medical record for scenarios associated with an increased risk of digoxin toxicity (renal insufficiency, drug-drug interaction, electrolyte deficiencies, or supra-therapeutic digoxin concentrations) and, if these conditions are present, warns the clinician in real-time, synchronous to the ordering process, suggesting measures to minimize digoxin toxicity (figure 6).

Similarly, for patients with active orders for digoxin, when new laboratory results are posted to the electronic medical record suggesting digoxin toxicity (i.e. elevated digoxin concentration) or the potential for digoxin toxicity (i.e. electrolyte deficiencies or worsening renal function), the CDS system alerts clinicians asynchronously by generating a printout at the patient's nursing station as well as an electronic communication (similar to an e-mail) to the patient's providers warning of the potential for digoxin toxicity. Utilizing this technology, potential cases of digoxin toxicity have been prevented<sup>[58]</sup> and inpatient prescribing of digoxin has improved.<sup>[60]</sup> While these computerized safeguards are currently only in place for patients who have been hospitalized, technology is being developed that could similarly prevent prescribing errors in ambulatory patients.

While technological advances such as automated CDS systems may reduce the incidence of digoxin toxicity, only a small minority of healthcare facilities utilize these advanced systems. In those healthcare settings without the benefit of advanced computer technology, education regarding the appropriate use of digoxin is critical in preventing medication errors that lead to digoxin toxicity. Given that renal insufficiency plays a significant role in the development of digoxin toxicity, educating clinicians on the importance of using the creatinine clearance as the preferred assessment of renal function (compared with serum creatinine) is important. We have found that clinicians sometimes assess renal function based on serum creatinine level alone rather than creatinine clearance. Consequently, they are more likely to overestimate renal function in women,<sup>[60]</sup> based on the 0.85 sex-based correction factor for women in the Cockcroft and Gault equation.<sup>[61]</sup> If clinicians rely solely on serum creatinine level to assess renal function, renal function in women may be overestimated, placing them at higher risk for digoxin toxicity.

## 6. Conclusion

Digoxin toxicity, once common, has declined for a variety of reasons including more accurate dosing methods and the routine availability of digoxin concentrations. Moreover, the results of large multicenter trials that have refined the role of digoxin, further characterization of drug interactions with digoxin, the

availability of more effective drugs for the treatment of heart failure, and the acceptance of a new (lower) therapeutic range can be expected to even further reduce the frequency of digoxin toxicity. Yet, digoxin toxicity still occurs and in the modern era most cases can and should be prevented. Many patients with digoxin toxicity are simply prescribed a dosage that is too high for their renal function or, alternatively, errors in prescribing or counseling occur. With modern technology, using tools such as CPOE and prompts that alert the clinician to the possibility of a prescribing error that could result in toxicity, it may be possible to all but eliminate digoxin toxicity making it a rare event in the future.

Digoxin toxicity was historically not only common but highly fatal. The commercial availability of digoxin immune Fab has provided a highly effective and life-saving treatment. It may be possible to expand the indications of these Fab fragments beyond life-threatening situations. In certain cases of non life-threatening toxicity, digoxin immune Fab can be cost effective, shortening hospital stay and reversing bothersome symptoms.

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### References

- Smith TW, Haber B. Digoxin intoxication: the relationship of clinical presentation to serum digoxin concentration. *J Clin Invest* 1970; 49: 2377-86
- Beller GA, Smith TW, Abelmann WH, et al. Digitalis intoxication: a prospective clinical study with serum level correlations. *N Engl J Med* 1971; 284: 989-97
- Duhme DW, Greenblatt DJ, Koch-Weser J. Reduction of digoxin toxicity associated with measurement of serum levels: a report from the Boston Collaborative Drug Surveillance Program. *Ann Intern Med* 1974; 80: 516-9
- Jelliffe R. A mathematical analysis of digitalis kinetics in patients with normal and reduced renal function. *Math Biosci* 1967; 1: 305-25
- Jelliffe RW. An improved method of digoxin therapy. *Ann Intern Med* 1968; 69: 703-17
- The Digitalis Investigation Group. The effect of digoxin on mortality and morbidity in patients with heart failure. *N Engl J Med* 1997; 336: 525-33
- Adams Jr KF, Gheorghiade M, Uretsky BF, et al. Clinical benefits of low serum digoxin concentrations in heart failure. *J Am Coll Cardiol* 2002; 39: 946-53
- Rathore SS, Curtis JP, Wang Y, et al. Association of serum digoxin concentration and outcomes in patients with heart failure. *JAMA* 2003; 289: 871-8
- Smith TW, Antman EM, Friedman PL, et al. Digitalis glycosides: mechanisms and manifestations of toxicity. Part I. *Prog Cardiovasc Dis* 1984; 26: 413-58
- Smith TW, Antman EM, Friedman PL, et al. Digitalis glycosides: mechanisms and manifestations of toxicity. Part II. *Prog Cardiovasc Dis* 1984; 26: 495-540
- Smith TW, Antman EM, Friedman PL, et al. Digitalis glycosides: mechanisms and manifestations of toxicity. Part III. *Prog Cardiovasc Dis* 1984; 27: 21-56
- Irons Jr GV, Orgain ES. Digitalis-induced arrhythmias and their management. *Prog Cardiovasc Dis* 1966; 8: 539-69
- Geering K. Na<sup>+</sup>-K<sup>+</sup>-ATPase. *Curr Opin Nephrol Hypertens* 1997 Sep; 6 (5): 434-9
- Eichhorn EJ, Gheorghiade M. Digoxin. *Prog Cardiovasc Dis* 2002; 44 (4): 251-66
- Hauptman PJ, Kelly RA. Digitalis. *Circulation* 1999; 99: 1265-70
- Kelly RA, Smith TW. Recognition and management of digitalis toxicity. *Am J Cardiol* 1992; 69: 108-8G
- Xie JT, Cunningham PM, January CT. Digoxin-induced delayed afterdepolarizations: biphasic effects of digoxin on action potential duration and the Q-T interval in cardiac Purkinje fibers. *Methods Find Exp Clin Pharmacol* 1995; 17: 113-20
- Rocchetti M, Besana A, Mostacciolo G, et al. Diverse toxicity associated with cardiac Na<sup>+</sup>/K<sup>+</sup> pump inhibition: evaluation of electrophysiological mechanisms. *J Pharmacol Exp Ther* 2003; 305: 765-71
- Krum H, Bigger Jr JT, Goldsmith RL, et al. Effect of long-term digoxin therapy on autonomic function in patients with chronic heart failure. *J Am Coll Cardiol* 1995; 25: 289-94
- Newton GE, Tong JH, Schofield AM, et al. Digoxin reduces cardiac sympathetic activity in severe congestive heart failure. *J Am Coll Cardiol* 1996; 28: 155-61
- Gheorghiade M, Ferguson D. Digoxin: a neurohormonal modulator in heart failure? *Circulation* 1991; 84: 2181-6
- Gheorghiade M, Hall VB, Jacobsen G, et al. Effects of increasing maintenance dose of digoxin on left ventricular function and neurohormones in patients with chronic heart failure treated with diuretics and angiotensin-converting enzyme inhibitors. *Circulation* 1995; 92: 1801-7
- Ieiri I, Takane H, Otsubo K. The MDR1 (ABCB1) gene polymorphism and its clinical implications. *Clin Pharmacokinet* 2004; 43 (9): 553-76
- Isalo E. Clinical pharmacokinetics of digoxin. *Clin Pharmacokinet* 1977; 2 (1): 1-16
- Fromm MF, Kim RB, Stein CM, et al. Inhibition of P-glycoprotein-mediated drug transport: a unifying mechanism to explain the interaction between digoxin and quinidine. *Circulation* 1999; 99: 552-7
- Yamreudeewong W, DeBisschop M, Martin LG, et al. Potentially significant drug interactions of class III antiarrhythmic drugs. *Drug Saf* 2003; 26: 421-38
- Kernan WN, Castellsague J, Perlman GD, et al. Incidence of hospitalization for digitalis toxicity among elderly Americans. *Am J Med* 1994; 96: 426-31
- Williamson KM, Thrasher KA, Fulton KB, et al. Digoxin toxicity: an evaluation in current clinical practice. *Arch Intern Med* 1998; 158: 2444-9
- Mahdyouon H, Battilana G, Rosman H, et al. The evolving pattern of digoxin intoxication: observations at a large urban hospital from 1980 to 1988. *Am Heart J* 1990; 120: 1189-94
- Rahmitoola SH. Digitalis therapy for patients in clinical heart failure. *Circulation* 2004; 109: 2942-6
- Gandhi AJ, Vlases PH, Morton DJ, et al. Economic impact of digoxin toxicity. *Pharmacoeconomics* 1997; 12: 175-81
- Hickey AR, Wenger TL, Carpenter VP, et al. Digoxin Immune Fab therapy in the management of digitalis intoxication: safety and efficacy results of an observational surveillance study. *J Am Coll Cardiol* 1991; 17: 590-8
- Abad-Santos F, Carcas AJ, Ibanez C, et al. Digoxin level and clinical manifestations as determinants in the diagnosis of digoxin toxicity. *Ther Drug Monit* 2000; 22: 163-8
- Ma G, Brady WJ, Pollack M, et al. Electrocardiographic manifestations: digitalis toxicity. *J Emerg Med* 2001; 20: 145-52
- Antman EM, Wenger TL, Butler Jr VP, et al. Treatment of 150 cases of life-threatening digitalis intoxication with digoxin-specific Fab antibody fragments: final report of a multicenter study. *Circulation* 1990; 81: 1744-52
- Sharff JA, Bayer MJ. Acute and chronic digitalis toxicity: presentation and treatment. *Ann Emerg Med* 1982; 11: 327-31
- Ekins BR, Watanabe AS. Acute digoxin poisonings: review of therapy. *Am J Hosp Pharm* 1978; 35: 268-77
- Park GD, Goldberg MJ, Spector R, et al. The effects of activated charcoal on digoxin and digitoxin clearance. *Drug Intell Clin Pharm* 1985; 19: 937-41
- Lalonde RL, Deshpande R, Hamilton PP, et al. Acceleration of digoxin clearance by activated charcoal. *Clin Pharmacol Ther* 1985; 37: 367-71
- Rawashdeh NM, al-Hadidi HF, Irshaid YM, et al. Gastrointestinal dialysis of digoxin using cholestyramine. *Pharmacol Toxicol* 1993; 72: 245-8
- Neuvonen PJ, Kivisto K, Hirvisalo EL. Effects of resins and activated charcoal on the absorption of digoxin, carbamazepine and frusemide. *Br J Clin Pharmacol* 1988; 25: 229-33
- Smith TW, Haber E, Yeatman L, et al. Reversal of advanced digoxin intoxication with Fab fragments of digoxin-specific antibodies. *N Engl J Med* 1976; 294: 797-800
- Flanagan RJ, Jones AL. Fab antibody fragments: some applications in clinical toxicology. *Drug Saf* 2004; 27: 1115-33

44. DiDomenico RJ, Walton SM, Sanoski CA, et al. Analysis of the use of digoxin immune fab for the treatment of non-life-threatening digoxin toxicity. *J Cardiovasc Pharmacol Ther* 2000; 5: 77-85
45. Bateman DN. Digoxin-specific antibody fragments: how much and when? *Toxicol Rev* 2004; 23: 135-43
46. Kaushal R, Bates DW, Landrigan C, et al. Medication errors and adverse drug events in pediatric inpatients. *JAMA* 2001; 285: 2114-20
47. Bates DW, Cullen DJ, Laird N, et al. Incidence of adverse drug events and potential adverse drug events: implications for prevention. ADE Prevention Study Group. *JAMA* 1995; 274: 29-34
48. Leape LL, Lawthers AG, Brennan TA, et al. Preventing medical injury. *QRB Qual Rev Bull* 1993; 19: 144-9
49. Bates DW, Leape LL, Petrycki S. Incidence and preventability of adverse drug events in hospitalized adults. *J Gen Intern Med* 1993; 8: 289-94
50. Bates DW, Boyle DL, Vander Vliet MB, et al. Relationship between medication errors and adverse drug events. *J Gen Intern Med* 1995; 10: 199-205
51. Bates DW, Leape LL, Cullen DJ, et al. Effect of computerized physician order entry and a team intervention on prevention of serious medication errors. *JAMA* 1998; 280: 1311-6
52. Potts AL, Barr FE, Gregory DF, et al. Computerized physician order entry and medication errors in a pediatric critical care unit. *Pediatrics* 2004; 113: 59-63
53. King WJ, Paice N, Rangrej J, et al. The effect of computerized physician order entry on medication errors and adverse drug events in pediatric inpatients. *Pediatrics* 2003; 112: 506-9
54. Kaushal R, Shojania KG, Bates DW. Effects of computerized physician order entry and clinical decision support systems on medication safety: a systematic review. *Arch Intern Med* 2003; 163: 1409-16
55. Evans RS, Pestotnik SL, Classen DC, et al. A computer-assisted management program for antibiotics and other anti-infective agents. *N Engl J Med* 1998; 338: 232-8
56. Falconnier AD, Haefeli WE, Schoenenberger RA, et al. Drug dosage in patients with renal failure optimized by immediate concurrent feedback. *J Gen Intern Med* 2001; 16: 369-75
57. Chertow GM, Lee J, Kuperman GJ, et al. Guided medication dosing for inpatients with renal insufficiency. *JAMA* 2001; 286: 2839-44
58. Galanter WL, DiDomenico RJ, Polikaitis A. Preventing exacerbation of an ADE with automated decision support. *J Healthc Inf Manag* 2002; 16: 44-9
59. Galanter WL, Polikaitis A, DiDomenico RJ. A trial of automated safety alerts for inpatient digoxin use with computerized physician order entry. *J Am Med Inform Assoc* 2004; 11: 270-7
60. Galanter WL, DiDomenico RJ, Polikaitis A. A trial of automated decision support alerts for contraindicated medications using computerized physician order entry. *J Am Med Inform Assoc* 2005; 12: 269-74
61. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron* 1976; 16: 31-41

Correspondence and offprints: Professor Jerry L. Bauman, University of Illinois at Chicago, m/c 886, 833 Wood Street, Chicago, Illinois 60612, USA.  
E-mail: jbauman@uic.edu



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## Overview of sudden cardiac arrest and sudden cardiac death

### Authors

David S Siscovick, MD  
Philip J Podrid, MD

### Section Editors

Brian Olshansky, MD  
Scott Manaker, MD, PhD

### Deputy Editor

Brian C Downey, MD, FACC

### Disclosures

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**INTRODUCTION** — Sudden cardiac arrest (SCA) and sudden cardiac death (SCD) refer to the sudden cessation of cardiac activity with hemodynamic collapse, typically due to sustained ventricular tachycardia/ventricular fibrillation. These events mostly occur in patients with structural heart disease (that may not have been previously diagnosed), particularly coronary heart disease. (See "[Pathophysiology and etiology of sudden cardiac arrest](#)".)

The event is referred to as SCA (or aborted SCD) if an intervention (eg, defibrillation) or spontaneous reversion restores circulation, and the event is called SCD if the patient dies [1]. However, the use of SCD to describe both fatal and nonfatal cardiac arrest persists by convention.

The specific causes of SCA vary with the population studied and patient age ([table 1](#)). SCA most commonly results from hemodynamic collapse due to ventricular fibrillation (VF) in the setting of structural heart disease ([figure 1](#)) [2]. (See "[Pathophysiology and etiology of sudden cardiac arrest](#)".)

The outcome following SCA depends upon numerous factors including the underlying cause and the rapidity of resuscitation. (See "[Supportive data for advanced cardiac life support in adults with sudden cardiac arrest](#)" and "[Outcome of sudden cardiac arrest](#)".)

Most individuals suffering from SCA become unconscious within seconds to minutes as a result of insufficient cerebral blood flow. There are usually no premonitory symptoms. If symptoms are present, they are nonspecific and include chest discomfort, palpitations, shortness of breath, and weakness.

**DEFINITIONS** — Various criteria have been used to define SCA and SCD in the medical literature [3]. Difficulties in deriving a specific definition include the following:

- Events are witnessed in only two-thirds of cases, making the diagnosis difficult to establish in many instances.
- It is not possible to restrict the definition of SCA to documented cases of VF since the cardiac rhythm at clinical presentation is unknown in many cases.

- The duration of symptoms prior to SCA generally defines the suddenness of death. However, the duration of symptoms is unknown in approximately one-third of cases.

For these reasons, operational criteria for SCA and SCD have been proposed that do not rely upon the cardiac rhythm at the time of the event. The criteria focus on the out-of-hospital occurrence of a presumed sudden pulseless condition and the **absence** of evidence of a noncardiac condition (eg, central airway obstruction, intracranial hemorrhage, pulmonary embolism) as the cause of cardiac arrest.

The 2006 American College of Cardiology/American Heart Association/Heart Rhythm Society (ACC/AHA/HRS) to establish data standards for electrophysiology included definitions to guide documentation in research and clinical practice.

The following definitions of SCA and SCD were presented:

"[Sudden] cardiac arrest is the sudden cessation of cardiac activity so that the victim becomes unresponsive, with no normal breathing and no signs of circulation. If corrective measures are not taken rapidly, this condition progresses to sudden death. Cardiac arrest should be used to signify an event as described above, that is reversed, usually by CPR and/or defibrillation or cardioversion, or cardiac pacing. Sudden cardiac death should not be used to describe events that are not fatal."

Throughout this topic we will use the terms SCA and SCD as defined in the 2006 ACC/AHA/HRS document. However, many continue to use SCD to describe both fatal and nonfatal cardiac arrest.

**EPIDEMIOLOGY** — Death certificate data suggest that SCD accounts for approximately 15 percent of the total mortality in the United States and other industrialized countries [4]. However, death certificate data may overestimate the prevalence of SCD [5,6]. In a prospective evaluation of deaths in one county in Oregon, SCD was implicated in 5.6 percent of annual mortality [5].

In absolute terms, the estimated number of sudden cardiac deaths in the United States in 1999 was approximately 450,000 [7]. Despite advances in the treatment of heart disease, the outcome of patients experiencing SCA remains poor, although the prognosis varies significantly according to the initial rhythm. (See "Outcome of sudden cardiac arrest".)

The risk of experiencing SCA is increased by a number of factors [4,6,8]. The incidence increases dramatically with age and with underlying cardiac disease (figure 2 and figure 3). In addition, men are two to three times more likely to experience SCA than women (figure 2)

The magnitude of the influence of underlying cardiac disease on the risk of SCA is illustrated by the following observations:

- The risk of SCA is increased six- to ten-fold in the presence of clinically recognized heart disease, and two- to four-fold in the presence of coronary heart disease (CHD) risk factors [6,9].
- SCD is the mechanism of death in over 60 percent of patients with known CHD [4,7,10]. In addition, SCA is the **initial** clinical manifestation of CHD in approximately

15 percent [11]. (See "Epidemiology of coronary heart disease", section on 'Sudden cardiac death'.)

**ETIOLOGY** — SCA usually occurs in people with some form of underlying structural heart disease, most notably CHD (table 1). The etiologies of SCA are discussed in detail separately, but will be briefly reviewed here. (See "Pathophysiology and etiology of sudden cardiac arrest".)

**Coronary heart disease** — As much as 70 percent of SCAs have been attributed to CHD. Among patients with CHD, SCA can occur both during an acute coronary syndrome (ACS) and in the setting of chronic, otherwise stable CHD (often such patients have had prior myocardial damage and scar that serves as a substrate for SCA). (See "Epidemiology of coronary heart disease" and "Clinical features and treatment of ventricular arrhythmias during acute myocardial infarction" and "Incidence of and risk stratification for sudden cardiac death after acute myocardial infarction".)

The arrhythmic mechanisms and the implications for SCA survivors are different in these two settings. (See "Outcome of sudden cardiac arrest".)

**Other structural heart disease** — Other forms of structural heart disease, both acquired and hereditary, account for approximately 10 percent of cases of out-of-hospital SCA. Examples of such disorders include the following:

- Heart failure and cardiomyopathy in which SCD is responsible for approximately one-third of deaths. (See "Ventricular arrhythmias in heart failure and cardiomyopathy".)
- Left ventricular hypertrophy due to hypertension or other causes. (See "Left ventricular hypertrophy and arrhythmia".)
- Myocarditis. (See "Clinical manifestations and diagnosis of myocarditis in adults", section on 'Clinicopathologic classification'.)
- Hypertrophic cardiomyopathy. (See "Ventricular arrhythmias and sudden cardiac arrest in hypertrophic cardiomyopathy".)
- Arrhythmogenic right ventricular cardiomyopathy. (See "Genetics and pathogenesis of arrhythmogenic right ventricular cardiomyopathy".)
- Congenital coronary artery anomalies. (See "Congenital and pediatric coronary artery abnormalities".)
- Mitral valve prolapse. (See "Natural history of chronic mitral regurgitation in mitral valve prolapse and flail mitral leaflet".)

**Absence of structural heart disease** — In different reports, approximately 10 to 12 percent of cases of SCA among subjects under age 45 occur in the absence of structural heart disease [12,13], while a lower value of about 5 percent has been described when older patients are included [14,15]. (See "Sudden cardiac arrest in the absence of apparent structural heart disease".)

This can occur in a variety of settings:

- Brugada syndrome. (See "Brugada syndrome".)

- Idiopathic VF, also called primary electrical disease. (See "Sudden cardiac arrest in the absence of apparent structural heart disease", section on 'Idiopathic VF'.)
- Congenital or acquired long QT syndrome (table 2). (See "Clinical features of congenital long QT syndrome" and "Acquired long QT syndrome".)
- Arrhythmogenic right ventricular cardiomyopathy. (See "Clinical manifestations of arrhythmogenic right ventricular cardiomyopathy".)
- Familial polymorphic ventricular tachycardia, also called "catecholaminergic polymorphic VT." (see "Catecholaminergic polymorphic ventricular tachycardia and other polymorphic ventricular tachycardias with a normal QT interval").)
- Familial SCD of uncertain cause.
- Wolff-Parkinson-White syndrome. (See "Tachyarrhythmias associated with accessory pathways", section on 'Ventricular fibrillation and sudden death'.)

**Acute triggers** — In addition to the presence of the above underlying disorders, superimposed triggers for SCA appear to play a major role in the pathogenesis of this disorder. These include ischemia, electrolyte disturbances (particularly hypokalemia and hypomagnesemia), the proarrhythmic effect of some antiarrhythmic drugs, autonomic nervous system activation, and psychosocial factors. (See "Evaluation of the survivor of sudden cardiac arrest", section on 'Transient or reversible causes'.)

In addition, SCA can result from commotio cordis in which VF is precipitated by direct trauma over precordium. (See "Sudden cardiac arrest in the absence of apparent structural heart disease", section on 'Commotio cordis'.)

**RISK FACTORS** — A number of clinical characteristics and other factors are associated with an increased risk of SCA among persons without prior clinically recognized heart disease [16-21]. Most risk factors for CHD are also risk factors for SCA. These include dyslipidemia, hypertension, cigarette smoking, physical inactivity, obesity, diabetes mellitus, and a family history of premature CHD or myocardial infarction (figure 4) [16-18,22,23]. (See "Overview of the risk factors for cardiovascular disease".)

**Cigarette smoking** — Current cigarette smoking and the number of cigarettes smoked per day among current smokers are strongly related to the risk of SCA in patients with CHD [24]. Based upon the observations that the risk of SCA is particularly high among current smokers and declines rapidly after stopping smoking, smoking cessation should be viewed as a critical component of efforts to reduce the risk of SCA as well as a multitude of other complications. (See "Cardiovascular risk of smoking and benefits of smoking cessation" and "Patterns of tobacco use and benefits of smoking cessation".)

**Exercise** — The risk of SCA is transiently increased during and up to 30 minutes after strenuous exercise compared to other times [18,25]. However, the actual risk during any one episode of vigorous exercise is very low (1 per 1.51 million episodes of exercise) [25]. Furthermore, the magnitude of the transient increase in risk during acute exercise is lower among men who are regular exercisers compared with men for whom exercise is unusual [18,25]. (See "Overview of the benefits and risks of exercise".)

The small transient increase in risk during exercise is **outweighed** by a reduction in the risk of SCA at other times [16,26]. Regular exercise is associated with a lower resting heart rate and increased heart rate variability, characteristics associated with a reduced risk of SCD (table 3). (See "Exercise and fitness in the prevention of cardiovascular disease".)

One exception to the lower overall risk associated with intensive exercise occurs in patients with certain, often unrecognized underlying heart diseases. Examples include hypertrophic cardiomyopathy, anomalous coronary artery of wrong sinus origin, myocarditis, and arrhythmogenic right ventricular cardiomyopathy [27,28]. (See "Risk of sudden cardiac death in athletes".)

**Family history of SCA** — A family history of SCA, either alone or with myocardial infarction, is associated with a 1.5 to 1.8-fold increased risk of SCA [17,23]. The increase in risk is not explained by traditional risk factors that tend to aggregate in families, such as hypercholesterolemia, hypertension, diabetes mellitus, and obesity.

The magnitude of the increase in risk associated with the presence of a family history is modest compared to the two- to five-fold increase in risk associated with other modifiable risk factors such as physical inactivity and current cigarette smoking. Few studies have examined potential gene-environment interactions related to the risk of SCD. Nevertheless, it is likely that interactions of mutations or polymorphisms in specific genes and environmental factors influence this risk.

**Serum CRP** — Chronic inflammation, as manifested in part by higher serum concentrations of C-reactive protein (CRP), has been implicated as a risk factor for a variety of cardiovascular diseases (including acute coronary syndromes, stroke, and the efficacy of lipid lowering with statins). Elevated serum CRP is also associated with an increased risk of SCA [29]. (See "C-reactive protein in cardiovascular disease".)

**Excess alcohol intake** — Moderate alcohol intake (eg, one to two drinks per day, and avoidance of binge drinking) may decrease the risk of SCD [30]. In comparison, heavy alcohol consumption (six or more drinks per day) or binge drinking **increases** the risk for SCD [30,31]. (See "Cardiovascular benefits and risks of moderate alcohol consumption".)

**Psychosocial factors** — Clinical observations have suggested a possible relation between acutely stressful situations and the risk of SCA. Major disasters, such as earthquakes and war, result in a rapid transient increase in the rate of SCA in populations [19,20]. The level of educational attainment and social support from others may alter the risk associated with stressful life events. (See "Psychosocial factors in sudden cardiac arrest".)

**Caffeine** — Excessive caffeine intake has been investigated as a potential risk factor for SCA [32]. In the limited data available, no significant association between caffeine intake and SCA have been found.

**Fatty acids** — Elevated plasma nonesterified fatty acid (free fatty acid) concentrations are associated with ventricular arrhythmias and SCD after a myocardial infarction and, after adjustment for confounding factors, in the general population [33]. In addition, cardiac arrest survivors without prior clinically recognized heart disease may have, when compared to controls, higher concentrations of total trans-fatty acids and of trans isomers of linoleic acid in red blood cell membranes [34]. (See "Dietary fat".)

In contrast, a higher intake and higher levels of long-chain n-3 polyunsaturated fatty acids (eicosapentaenoic acid and docosahexaenoic acid) in plasma and the red blood cell

membrane are associated with a **lower** risk of SCD [21,35-37]. (See 'Fish intake and fish oil' below.)

**MANAGEMENT** — The acute management of cardiac arrest is discussed in detail separately. (See "Supportive data for advanced cardiac life support in adults with sudden cardiac arrest".)

Management issues for survivors of SCA include the following:

- Identification and treatment of acute reversible causes
- Evaluation for structural heart disease
- In patients without obvious arrhythmic triggers or cardiac structural abnormalities, an evaluation for primary electrical diseases
- Neurologic and psychologic assessment
- In selected patients with a suspected or confirmed heritable syndrome, evaluation of family members

These issues are discussed in detail separately. (See "Evaluation of the survivor of sudden cardiac arrest".)

**PRIMARY PREVENTION** — The optimal approach to the primary prevention of SCA varies among the following categories:

- The general population.
- Patients surviving an acute myocardial infarction. (See "Incidence of and risk stratification for sudden cardiac death after acute myocardial infarction".)
- Patients with heart failure and cardiomyopathy. (See "Ventricular arrhythmias in heart failure and cardiomyopathy".)
- Patients with one of the congenital disorders associated with an increased risk of SCA (eg, Brugada syndrome, congenital long QT syndrome, WPW).

**General population** — There are two approaches to reduce the risk of SCA in the general population:

- Screening and risk stratification to identify individuals who may benefit from specific interventions (eg, stress testing, screening ECGs).
- Interventions that may be expected to reduce SCA risk in any individual (eg, smoking cessation or other lifestyle modifications). Such interventions generally target the underlying disorders that predispose to SCA.

**Screening and risk stratification** — Among populations already known to be at an elevated risk of SCA (eg, patients with a prior myocardial infarction), further risk stratification with a variety of tests can identify subgroups that benefit from specific therapies, such as an ICD. (See 'Post myocardial infarction' below.)

However, in the general population without known cardiovascular disease, there is no evidence that routine screening with any test (eg, 12-lead electrocardiography, exercise stress testing, or Holter monitoring) effectively identifies populations at an increased risk of SCA.

With regard to risk stratification of the general population, we suggest the following:

- Screening for risk factors for cardiovascular disease according to standard guidelines. (See "[Screening guidelines for dyslipidemia](#)".) The USPSTF clinical practice guideline for screening for high blood pressure, as well as other USPSTF guidelines, can be accessed through the website for the Agency for Healthcare Research and Quality at [www.ahrq.gov/clinic/uspstfix.htm](http://www.ahrq.gov/clinic/uspstfix.htm).
- Screening for CHD as appropriate in selected patients, according to standard guidelines. (See "[Screening for coronary heart disease](#)".)
- Routine additional testing for the purpose of SCA risk stratification is not recommended.

An issue that merits special consideration is the pre-participation evaluation of athletes. This is a complex issue and there are conflicting opinions regarding the appropriate nature of a screening evaluation. (See "[Screening to prevent sudden death in athletes](#)".)

**Risk factor reduction** — Many of the traditional risk factors associated with the development of CHD are also associated with SCA. (See '[Risk factors](#)' above and "[Overview of primary prevention of coronary heart disease and stroke](#)".)

Thus, management of these risk factors may reduce the incidence of SCA in the general public. Such interventions include:

- Effective treatment of hypercholesterolemia
- Effective treatment of hypertension
- Adoption of a heart-healthy diet
- Regular exercise
- Smoking cessation
- Moderation of alcohol consumption
- Effective treatment of diabetes

These interventions are generally in agreement with guidelines published in 2001 by a task force of the European Society of Cardiology [38].

There is no definitive evidence that risk factor reduction in the general population lowers the rate of SCA. However, a number of studies have demonstrated that interventions to treat risk factors can lower total cardiovascular and coronary mortality. Since the majority of CHD mortality is due to SCD, these results suggest that interventions to reduce risk factors will reduce SCA rates as well. (See "[Overview of primary prevention of coronary heart disease and stroke](#)".)

As an example, a multifactorial, controlled, randomized trial from the Belgian component of the World Health Organization evaluated the effect of efforts aimed at reducing serum cholesterol (via dietary changes), increasing physical activity, and controlling smoking, hypertension, and weight (in those who were overweight) on risk factors and mortality [39]. Compared to the control group, the intervention group had significant reductions in the incidence of CHD and coronary mortality.

**Moderate alcohol intake** — Excess alcohol intake increases the risk of SCA, while light-to-moderate alcohol consumption (ie,  $\leq 2$  drinks per day) reduces the risk of coronary heart disease and cardiovascular mortality [30,31]. (See '[Excess alcohol intake](#)' above.)

It is reasonable to expect that moderate alcohol intake will also reduce SCA. This effect was documented by the Physicians Health Study, which evaluated 21,537 men who were free of known cardiovascular disease [30]. Compared to men who rarely or never drank, those who had two to four drinks per week or five to six drinks per week had a significantly reduced risk for SCD (relative risks 0.40 and 0.21, respectively); the risk approached unity at  $\geq 2$  drinks per day. (See "Cardiovascular benefits and risks of moderate alcohol consumption".)

**Regular exercise** — There are no data from long-term exercise intervention trials among apparently healthy persons that focus upon major disease end points. Nevertheless, regular exercise should be encouraged for the primary prevention of CHD and SCA. Although there is a small transient increase in risk during and shortly after strenuous exercise, there is an overall reduction in SCD among exercisers compared with sedentary men [16,18,26,40]. It is unclear if more exercise (higher intensity or longer duration) is better than less (non-strenuous physical activity, such as walking for exercise 30 minutes most days). (See 'Exercise' above and "Overview of the benefits and risks of exercise" and "Exercise and fitness in the prevention of cardiovascular disease".)

Patients should be advised to pay attention to potential symptoms of CHD, even if they have engaged in regular exercise without limitations for an extended period of time. In addition, patients with known heart disease should be encouraged to engage in regular exercise in a supervised setting such as a cardiac rehabilitation program. (See "Components of cardiac rehabilitation and exercise prescription".)

**Fish intake and fish oil** — In observational studies of populations at low cardiovascular risk, greater dietary fatty fish intake was associated with lower cardiac mortality [21,36,37,41,42]. This benefit is due in part to a reduced risk of SCD (figure 5). Based upon these results, subsequent randomized trials evaluated the benefit of fish oil supplements in various high-risk populations [43,44]. These issues are discussed in detail separately. (See "Lipid lowering with diet or dietary supplements", section on 'Fish oil' and "Role of implantable cardioverter-defibrillators for the secondary prevention of sudden cardiac death", section on 'Fish oil'.)

For most individuals, there is little evidence that the pharmacologic doses of n-3 polyunsaturated fatty acids found in fish oil supplements (approximately 10 to 20 times the nutritional dose from fish) provide more protection than the intake of one to two servings of fatty fish (eg, salmon) per week. The pharmacologic use of fish oils supplements should be restricted to patients with refractory hypertriglyceridemia and, in such patients, the periodic monitoring of apolipoprotein B levels is recommended. (See "Prudent diet" and "Approach to the patient with hypertriglyceridemia", section on 'Pharmacologic therapy (including fish oil)').

**Post myocardial infarction** — Patients who have had an MI are at an increased risk of SCA. However, among post-MI patients, this risk varies significantly according to a number of factors.

The approach to the prevention of SCA in such patients includes the following:

- Standard medical therapies. Both beta blockers and ACE inhibitors (or angiotensin II receptor blockers) reduce overall mortality after an MI and are routinely administered. These agents also lower the incidence of SCD. (See "Role of implantable cardioverter-

defibrillators for the primary prevention of sudden cardiac death after myocardial infarction", section on 'Medical therapy'.)

- Risk stratification to identify those patients at the highest risk of SCA. (See "Incidence of and risk stratification for sudden cardiac death after acute myocardial infarction".)
- ICD implantation in selected patients. (See "Role of implantable cardioverter-defibrillators for the primary prevention of sudden cardiac death after myocardial infarction".)

**Heart failure and cardiomyopathy** — Patients with heart failure and left ventricular systolic dysfunction, regardless of the etiology, are at an increased risk of SCA. Primary prevention with an ICD is recommended in selected patients with either ischemic or nonischemic cardiomyopathy. The supporting data are discussed in detail separately. (See "Secondary and primary prevention of sudden cardiac death in heart failure and cardiomyopathy", section on 'Primary prevention of SCD'.)

In addition, as with patients with CHD, standard medical therapies for HF may lower the risk of SCA. (See "Ventricular arrhythmias in heart failure and cardiomyopathy", section on 'Effect of HF therapy on ventricular arrhythmia'.)

**Counseling patients and families** — Given the mounting evidence related to the primary prevention of SCA, it now is clear that primary care physicians can influence the occurrence of these events. As discussed above, there are clinical recommendations for those at risk of SCA that are likely to reduce risk. (See 'Risk factor reduction' above.)

## **SECONDARY PREVENTION**

**ICD therapy** — An implantable cardioverter-defibrillator (ICD) is the preferred therapeutic modality in most survivors of SCA. The ICD does not prevent the recurrence of malignant ventricular arrhythmias, but it effectively terminates these arrhythmias when they do recur. The role of the ICD in survivors of SCA is presented separately. (See "Role of implantable cardioverter-defibrillators for the secondary prevention of sudden cardiac death".)

ICD patients who have frequent arrhythmia recurrences and device discharges may benefit from adjunctive therapies, such as antiarrhythmic drugs or catheter ablation. (See "Role of implantable cardioverter-defibrillators for the secondary prevention of sudden cardiac death", section on 'Adjunctive therapy' and "Pharmacologic therapy in survivors of sudden cardiac arrest", section on 'Adjunctive therapy in patients with an ICD' and "Catheter ablation for ventricular arrhythmias".)

**Antiarrhythmic drugs** — Antiarrhythmic drugs are less effective than an ICD for secondary prevention of SCD. Thus, their use in this setting is limited to the adjunctive role described above, or in patients who do not want or are not candidates for an ICD (eg, due to marked comorbidities or end-stage heart failure that make death likely). (See "Pharmacologic therapy in survivors of sudden cardiac arrest".)

**SUMMARY AND RECOMMENDATIONS** — The following summary and recommendations address general issues related to SCA and SCD.

### **General information**

- SCA and SCD refer to the sudden cessation of cardiac activity with hemodynamic collapse. Events that are successfully treated with patient survival are referred to as SCA, while those that lead to death are referred to as SCD. (See 'Definitions' above.)
- SCD is common, accounting for up to 15 percent of total mortality in industrialized countries, based upon review of death certificate data. Smaller prospective studies, however, have suggested a lower incidence. (See 'Epidemiology' above.)
- SCA is most commonly due to ventricular tachyarrhythmias. The risk of such arrhythmic events is increased in patients with coronary heart disease or other forms of structural heart disease. In patients with hearts that appear structurally normal, relatively uncommon primary arrhythmia syndromes can cause SCA. (See 'Etiology' above and "Pathophysiology and etiology of sudden cardiac arrest".)
- The risk factors for SCA are similar to those for coronary heart disease. (See 'Risk factors' above.)

**Primary prevention** — The approach to primary prevention of SCD varies according to a patient's clinical profile.

For the general population without known cardiac disease:

- Apart from standard screening and management of risk factors for CHD (eg, measurement of lipids and BP), in patients without known cardiac disease we recommend no additional screening tests or treatment for the purpose of primary prevention of SCD (**Grade 1B**). (See 'General population' above.)
- Preparticipation screening of athletes for the purpose of preventing SCD is a unique issue that is discussed in detail separately. (See "Screening to prevent sudden death in athletes".)

Patients with known cardiac disease (eg, prior MI, cardiomyopathy, or heart failure) are at an increased risk of SCA. (See 'Post myocardial infarction' above and 'Heart failure and cardiomyopathy' above.)

The approach to the primary prevention of SCA in such patients includes the following:

- Standard medical therapies that lower the incidence of SCD. (See "Role of implantable cardioverter-defibrillators for the primary prevention of sudden cardiac death after myocardial infarction", section on 'Medical therapy' and "Ventricular arrhythmias in heart failure and cardiomyopathy", section on 'Effect of HF therapy on ventricular arrhythmia'.)
- Testing for the purpose of SCA risk stratification in selected subgroups. (See "Incidence of and risk stratification for sudden cardiac death after acute myocardial infarction".)
- ICD implantation in selected patients. (See "Role of implantable cardioverter-defibrillators for the primary prevention of sudden cardiac death after myocardial infarction" and "Ventricular arrhythmias in heart failure and cardiomyopathy", section on 'Prevention of SCD'.)

**Management and secondary prevention** — The management of SCA includes acute treatment of the arrest, and for SCA survivors, a comprehensive evaluation and secondary prevention.

- The acute management of SCA involves standard cardiopulmonary resuscitation protocols. These issues are discussed in detail separately. (See "Supportive data for advanced cardiac life support in adults with sudden cardiac arrest".)
- Management of survivors of SCA includes the identification and treatment of acute reversible causes, evaluation for structural heart disease and/or primary electrical diseases, neurologic and psychologic assessment, and evaluation of family members in selected cases. These issues are discussed in detail separately. (See "Evaluation of the survivor of sudden cardiac arrest".)
- Secondary prevention of SCD, usually with an ICD, is appropriate for most SCA survivors. This issue is discussed in detail separately. (See "Role of implantable cardioverter-defibrillators for the secondary prevention of sudden cardiac death".)

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## REFERENCES

1. American College of Cardiology/American Heart Association Task Force on Clinical Data Standards (ACC/AHA/HRS Writing Committee to Develop Data Standards on Electrophysiology), Buxton AE, Calkins H, et al. ACC/AHA/HRS 2006 key data elements and definitions for electrophysiological studies and procedures: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Data Standards (ACC/AHA/HRS Writing Committee to Develop Data Standards on Electrophysiology). Circulation 2006; 114:2534.
2. Demirovic J, Myerburg RJ. Epidemiology of sudden coronary death: an overview. Prog Cardiovasc Dis 1994; 37:39.
3. Siscovick DS. Challenges in cardiac arrest research: data collection to assess outcomes. Ann Emerg Med 1993; 22:92.
4. Zheng ZJ, Croft JB, Giles WH, Mensah GA. Sudden cardiac death in the United States, 1989 to 1998. Circulation 2001; 104:2158.
5. Chugh SS, Jui J, Gunson K, et al. Current burden of sudden cardiac death: multiple source surveillance versus retrospective death certificate-based review in a large U.S. community. J Am Coll Cardiol 2004; 44:1268.
6. Rea TD, Pearce RM, Raghunathan TE, et al. Incidence of out-of-hospital cardiac arrest. Am J Cardiol 2004; 93:1455.
7. Centers for Disease Control and Prevention (CDC). State-specific mortality from sudden cardiac death--United States, 1999. MMWR Morb Mortal Wkly Rep 2002; 51:123.
8. Kannel WB, Wilson PW, D'Agostino RB, Cobb J. Sudden coronary death in women. Am Heart J 1998; 136:205.
9. Kuller LH. Sudden death--definition and epidemiologic considerations. Prog Cardiovasc Dis 1980; 23:1.
10. Gillum RF. Sudden coronary death in the United States: 1980-1985. Circulation 1989; 79:756.

11. Kannel WB, Doyle JT, McNamara PM, et al. Precursors of sudden coronary death. Factors related to the incidence of sudden death. *Circulation* 1975; 51:606.
12. Drory Y, Turetz Y, Hiss Y, et al. Sudden unexpected death in persons less than 40 years of age. *Am J Cardiol* 1991; 68:1388.
13. Topaz O, Edwards JE. Pathologic features of sudden death in children, adolescents, and young adults. *Chest* 1985; 87:476.
14. Chugh SS, Kelly KL, Titus JL. Sudden cardiac death with apparently normal heart. *Circulation* 2000; 102:649.
15. Survivors of out-of-hospital cardiac arrest with apparently normal heart. Need for definition and standardized clinical evaluation. Consensus Statement of the Joint Steering Committees of the Unexplained Cardiac Arrest Registry of Europe and of the Idiopathic Ventricular Fibrillation Registry of the United States. *Circulation* 1997; 95:265.
16. Siscovick DS, Weiss NS, Hallstrom AP, et al. Physical activity and primary cardiac arrest. *JAMA* 1982; 248:3113.
17. Friedlander Y, Siscovick DS, Weinmann S, et al. Family history as a risk factor for primary cardiac arrest. *Circulation* 1998; 97:155.
18. Siscovick DS, Weiss NS, Fletcher RH, Lasky T. The incidence of primary cardiac arrest during vigorous exercise. *N Engl J Med* 1984; 311:874.
19. Trichopoulos D, Katsouyanni K, Zavitsanos X, et al. Psychological stress and fatal heart attack: the Athens (1981) earthquake natural experiment. *Lancet* 1983; 1:441.
20. Kark JD, Goldman S, Epstein L. Iraqi missile attacks on Israel. The association of mortality with a life-threatening stressor. *JAMA* 1995; 273:1208.
21. Siscovick DS, Raghunathan TE, King I, et al. Dietary intake and cell membrane levels of long-chain n-3 polyunsaturated fatty acids and the risk of primary cardiac arrest. *JAMA* 1995; 274:1363.
22. Kannel WB, Thomas HE Jr. Sudden coronary death: the Framingham Study. *Ann N Y Acad Sci* 1982; 382:3.
23. Jouven X, Desnos M, Guerot C, Ducimetière P. Predicting sudden death in the population: the Paris Prospective Study I. *Circulation* 1999; 99:1978.
24. Goldenberg I, Jonas M, Tenenbaum A, et al. Current smoking, smoking cessation, and the risk of sudden cardiac death in patients with coronary artery disease. *Arch Intern Med* 2003; 163:2301.
25. Albert CM, Mittleman MA, Chae CU, et al. Triggering of sudden death from cardiac causes by vigorous exertion. *N Engl J Med* 2000; 343:1355.
26. Lemaitre RN, Siscovick DS, Raghunathan TE, et al. Leisure-time physical activity and the risk of primary cardiac arrest. *Arch Intern Med* 1999; 159:686.
27. Maron BJ, Carney KP, Lever HM, et al. Relationship of race to sudden cardiac death in competitive athletes with hypertrophic cardiomyopathy. *J Am Coll Cardiol* 2003; 41:974.
28. Corrado D, Basso C, Schiavon M, Thiene G. Screening for hypertrophic cardiomyopathy in young athletes. *N Engl J Med* 1998; 339:364.
29. Albert CM, Ma J, Rifai N, et al. Prospective study of C-reactive protein, homocysteine, and plasma lipid levels as predictors of sudden cardiac death. *Circulation* 2002; 105:2595.
30. Albert CM, Manson JE, Cook NR, et al. Moderate alcohol consumption and the risk of sudden cardiac death among US male physicians. *Circulation* 1999; 100:944.

31. Wannamethee G, Shaper AG. Alcohol and sudden cardiac death. *Br Heart J* 1992; 68:443.
32. Weinmann S, Siscovick DS, Raghunathan TE, et al. Caffeine intake in relation to the risk of primary cardiac arrest. *Epidemiology* 1997; 8:505.
33. Jouven X, Charles MA, Desnos M, Ducimetière P. Circulating nonesterified fatty acid level as a predictive risk factor for sudden death in the population. *Circulation* 2001; 104:756.
34. Lemaitre RN, King IB, Raghunathan TE, et al. Cell membrane trans-fatty acids and the risk of primary cardiac arrest. *Circulation* 2002; 105:697.
35. Harper CR, Jacobson TA. The fats of life: the role of omega-3 fatty acids in the prevention of coronary heart disease. *Arch Intern Med* 2001; 161:2185.
36. Albert CM, Campos H, Stampfer MJ, et al. Blood levels of long-chain n-3 fatty acids and the risk of sudden death. *N Engl J Med* 2002; 346:1113.
37. Daviglius ML, Stamler J, Orenca AJ, et al. Fish consumption and the 30-year risk of fatal myocardial infarction. *N Engl J Med* 1997; 336:1046.
38. Priori SG, Aliot E, Blomstrom-Lundqvist C, et al. Task Force on Sudden Cardiac Death of the European Society of Cardiology. *Eur Heart J* 2001; 22:1374.
39. De Backer G, Kornitzer M, Dramaix M, et al. The Belgian Heart Disease Prevention Project: 10-year mortality follow-up. *Eur Heart J* 1988; 9:238.
40. Shephard RJ, Balady GJ. Exercise as cardiovascular therapy. *Circulation* 1999; 99:963.
41. Kromhout D, Bosschieter EB, de Lezenne Coulander C. The inverse relation between fish consumption and 20-year mortality from coronary heart disease. *N Engl J Med* 1985; 312:1205.
42. Albert CM, Hennekens CH, O'Donnell CJ, et al. Fish consumption and risk of sudden cardiac death. *JAMA* 1998; 279:23.
43. Marchioli R, Barzi F, Bomba E, et al. Early protection against sudden death by n-3 polyunsaturated fatty acids after myocardial infarction: time-course analysis of the results of the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI)-Prevenzione. *Circulation* 2002; 105:1897.
44. Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-Prevenzione trial. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico. *Lancet* 1999; 354:447.

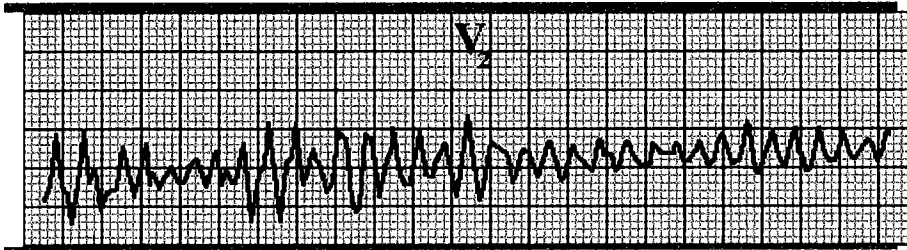
## GRAPHICS

### Major causes of sudden cardiac death

<b>Ischemic heart disease</b>
Coronary artery disease with myocardial infarction or angina
Coronary artery embolism
Nonatherogenic coronary artery disease (arteritis, dissection, congenital coronary artery anomalies)
Coronary artery spasm
<b>Nonischemic heart disease</b>
Hypertrophic cardiomyopathy
Dilated cardiomyopathy
Valvular heart disease
Congenital heart disease
Arrhythmogenic right ventricular dysplasia
Myocarditis
Acute pericardial tamponade
Acute myocardial rupture
Aortic dissection
<b>No structural heart disease</b>
Primary electrical disease (idiopathic ventricular fibrillation)
Brugada syndrome (right bundle branch block and ST segment elevation in leads V1 to V3)
Long QT syndrome
Preexcitation syndrome
Complete heart block
Familial sudden cardiac death
Chest wall trauma (commotio cordis)
<b>Noncardiac disease</b>
Pulmonary embolism
Intracranial hemorrhage
Drowning
Pickwickian syndrome
Drug-induced

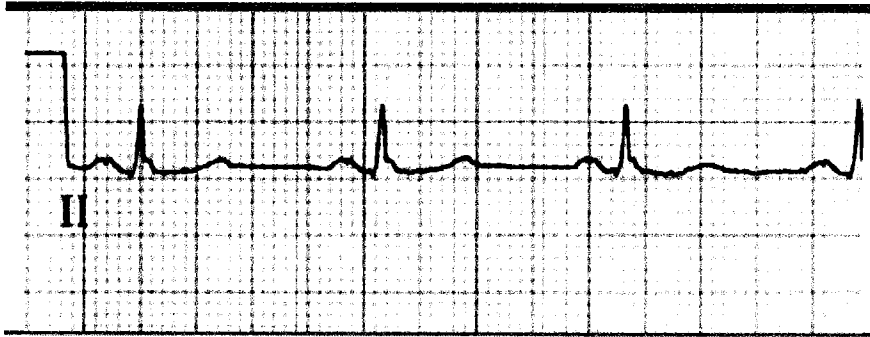
Central airway obstruction
Sudden infant death syndrome

### Ventricular fibrillation



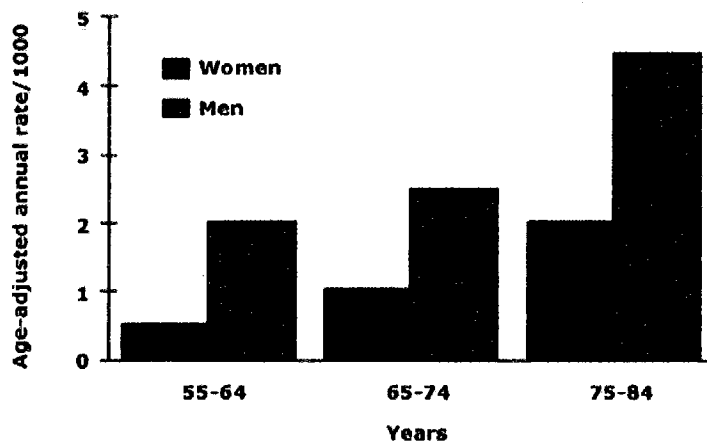
There is a complete absence of properly formed QRS complexes and no obvious P waves. A recent onset (eg, within minutes) of the arrhythmia is suggested by the coarse morphology of the fibrillatory waves.

### Normal rhythm strip



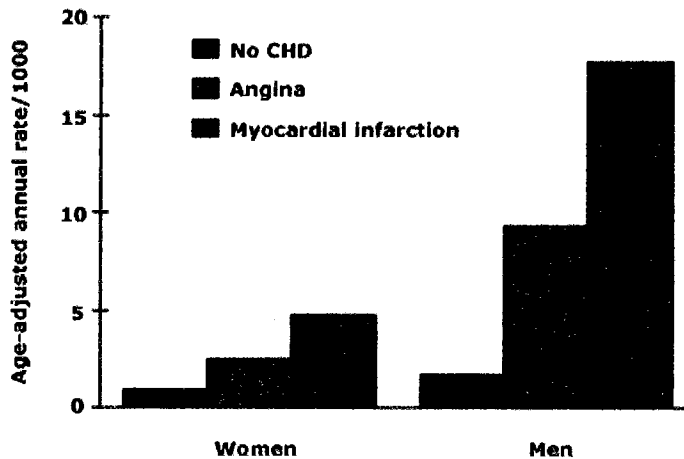
Normal rhythm strip in lead II. The PR interval is 0.15 sec and the QRS duration is 0.08 sec. Both the P and T waves are upright. *Courtesy of Morton F Arnsdorf, MD.*

### Incidence of sudden death in men and women increases with age



During a 38 years follow-up of subjects in the Framingham Heart Study, the annual incidence of sudden death increased with age in both men and women. However, at each age, the incidence of sudden death is higher in men than women. *Data from Kannel, WB, Wilson, PWF, D'Agostino, RB, et al, Am Heart J 1998; 136:205.*

## Risk of SCD is related to clinical manifestations of CHD



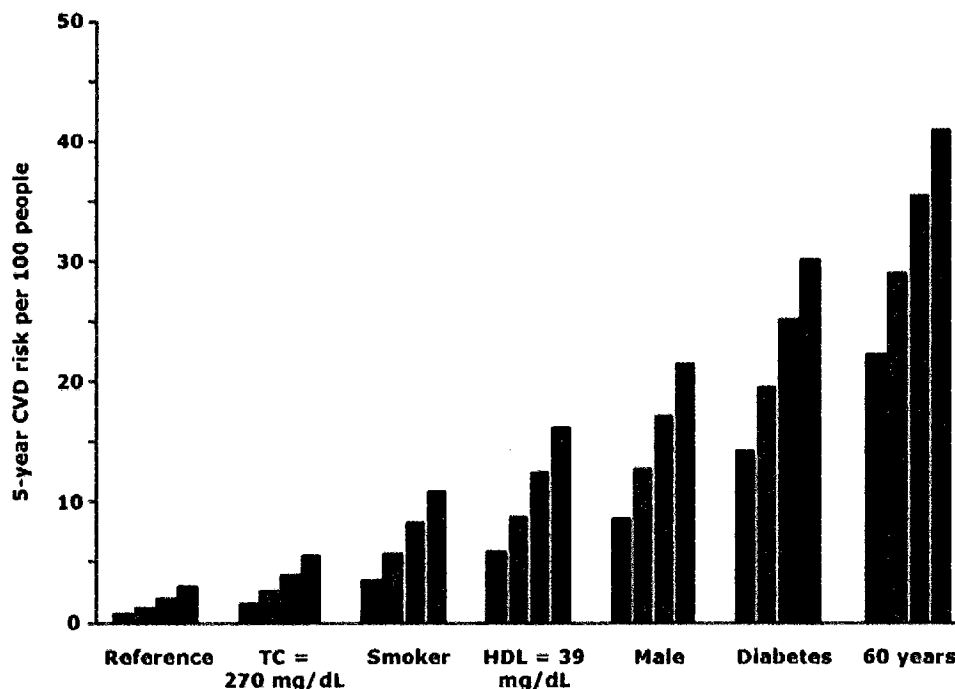
During a 38 year follow-up of subjects in the Framingham Heart Study, the annual incidence of sudden cardiac death (SCD) in both men and women was related to the clinical manifestations of coronary heart disease (CHD). It was highest in those with a myocardial infarction, intermediate in those with angina and no prior infarction, and lowest in those without overt CHD. *Data from Kannel, WB, Wilson, PWF, D'Agostino, RB, et al, Am Heart J 1998; 136:205.*

## Some reported causes and potentiators of the long QT syndrome

Congenital	Acquired (continued)
Jervell and Lange-Nielsen syndrome (including "channelopathies")  Romano-Ward syndrome  Idiopathic	<b>Antihistamines</b>
<b>Acquired</b>	Terfenadine
<b>Metabolic disorders</b>	Astemizole
Hypokalemia	<b>Psychotropic drugs</b>
Hypomagnesemia	Thioridazine
Hypocalcemia	Phenothiazines
Starvation	Tricyclic or tetracyclic antidepressants
Anorexia nervosa	Haloperidol and other butyrophenones
Liquid protein diets	<b>Antineoplastic agents</b>
Hypothyroidism	Dasatinib, eribulin, nilotinib, romidepsin, sorafenib, sunitinib, vandetanib, vorinostat
<b>Bradyarrhythmias</b>	<b>Other drugs</b>
Sinus node dysfunction	Selective serotonin reuptake inhibitors
AV block - second or third degree	Risperidone
<b>Antiarrhythmic drugs</b>	Methadone
Quinidine	Vasodilators - prenylamine, bepridil, mibefradil
Procainamide or N-acetylprocainamide	Diuretics - via electrolyte changes (esp. hypokalemia or hypomagnesemia)
Disopyramide	Serotonin antagonist - ketanserin
Amiodarone and dronedarone	Motility drugs - cisapride, domperidone
Sotalol	Droperidol - may be safe at the low doses used by anesthesiologists (0.625 to 1.25 mg)
Dofetilide, ibutilide, azimilide, sotalol	Ranolazine
Antimicrobial drugs	HIV protease inhibitors
Erythromycin, clarithromycin, telithromycin, azithromycin (minor)	Miscellaneous - organophosphate insecticides, probucol, cocaine, terodiline, papaverine, certain Chinese herbs, chloral hydrate, arsenic trioxide, cesium chloride, levomethadyl
Pentamidine	<b>Other factors</b>
Some azole antifungals - voriconazole, posaconazole	Myocardial ischemia or infarction, esp. with prominent T wave inversions
	Intracranial disease
	HIV infection
	Hypothermia

Some fluoroquinolones (eg, sparfloxacin, gatifloxacin, levofloxacin, moxifloxacin)	Connective tissue diseases with anti-Ro/SSA antibodies
Other - spiramycin, chloroquine, halofantrine, mefloquine	

## Cumulative absolute risk of CVD at five years



Cumulative absolute risk of cardiovascular disease (CVD) at five years according to systolic blood pressure and specified levels of other risk factors. The reference category is a nondiabetic, nonsmoking 50 year-old woman with a serum total cholesterol (TC) of 154 mg/dL (4.0 mmol/L) and HDL-cholesterol of 62 mg/dL (1.6 mmol/L). The CVD risks are given for systolic blood pressure levels of 110, 130, 150, and 170 mmHg. In the other categories, the additional risk factors are added consecutively. As an example, the diabetes category is a 50-year-old diabetic man who is a smoker and has a total cholesterol (TC) of 270 mg/dL (7 mmol/L) and HDL-cholesterol of 39 mg/dL (1 mmol/L). Adapted from Jackson, R, Lawes, CM, Bennett, DA, et al, *Lancet* 2005; 365:434

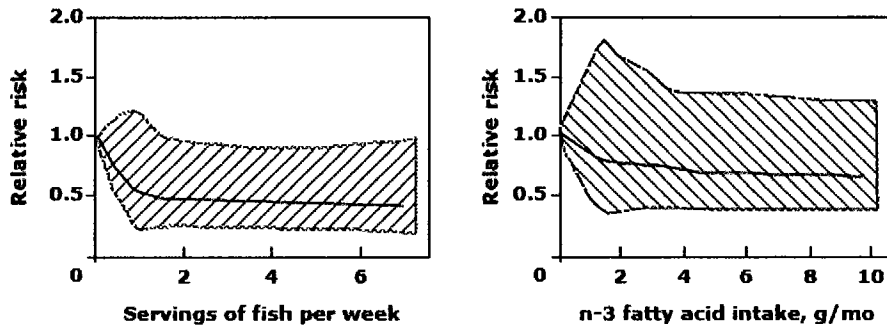
## Possible biologic mechanisms for exercise-induced reductions in all-cause and cardiac mortality

<p><b>Cardiovascular influences</b></p> <p>Reduction of resting and exercise heart rate</p> <p>Reduction of resting and exercise blood pressure</p> <p>Reduction of myocardial oxygen demand at submaximal levels of physical activity</p> <p>Expansion of plasma volume</p> <p>Increase in myocardial contractility</p> <p>Increase in peripheral venous tone</p> <p>Favorable changes in fibrinolytic system</p> <p>Increased endothelium-dependent vasodilation</p> <p>Increased gene expression for nitric oxide synthase</p> <p>Enhanced parasympathetic tone</p> <p>Possible increases in coronary blood flow, coronary collateral vessels, and myocardial capillary density</p>
<p><b>Metabolic influences</b></p> <p>Reduction of obesity</p> <p>Enhanced glucose tolerance</p> <p>Improved lipid profile</p>
<p><b>Lifestyle influences</b></p> <p>Decreased likelihood of smoking</p> <p>Possible reduction of stress</p> <p>Short-term reduction of appetite</p>

Data from Shepard, RJ, Balady, GJ, *Circulation* 1999; 99:963.

3-126

## The consumption of fish and fish oil reduces the risk of sudden death



The Physicians' Health Study of 20,551 men without evidence of heart disease, followed for up to 11 years, found that the risk of sudden death decreased as the weekly intake of fish and the monthly consumption of n-3 fatty acid increased. The hatched area represent pointwise 95 percent confidence intervals for the relative hazard function. Data from: Albert, CM, Hennekens, CH, O'Donnell, CJ, et al. JAMA 1998; 279:23.

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T. E. Vorpahl,<sup>1</sup> M.D. and J. I. Coe,<sup>2</sup> M.D.

## Correlation of Antemortem and Postmortem Digoxin Levels

The dynamics of digoxin metabolism have been well studied since the introduction of sensitive radioimmunoassay procedures capable of detecting low biologic levels of this compound [1]. The value of monitoring digoxin therapy through serum levels has been widely accepted, and toxic effects are frequently observed when the serum level of adult individuals exceeds 2 ng/ml [2,3]. Beller et al [4] reported a twofold increase in mortality among hospitalized patients having digitalis toxicity.

Only a few authors have reported on postmortem digoxin levels. Several of these have assumed that serum levels obtained from intracavitary myocardial autopsy specimens accurately reflect antemortem levels at the time of death [5-7]. Others have noted possible difficulties in interpreting postmortem values. Iisalo and Nuutila [8] in 1973 pointed out discrepancies between antemortem and postmortem serum digoxin levels in three cases and attributed this to "accumulated absorption," presumably prior to death. Karjalainen et al [9] in 1974 stated "the postmortem concentrations of blood digoxin are higher than those measured during life" but gave no explanatory or supporting data. Selesky et al [10] also thought that some of the elevated postmortem digoxin values seen in their series may have been due to the interval between death and sampling, although in the one case in which an antemortem specimen was analyzed there was no difference in value between the serum obtained before death and that taken at autopsy.

Holt and Benstead [11] in 1975 reported another problem with the interpretation of postmortem digoxin values. They demonstrated that digoxin levels on serum taken from heart blood at autopsy were consistently higher than levels on samples from the femoral veins, with the difference as great as 137% in their series. Dickson and Blazey [12] in 1977 stated they found a similar heart to venous blood ratio in one case and pointed out that most previous reports had not indicated the site from which the serum samples were obtained.

The purpose of the present study is fourfold: to determine the discrepancies that exist between antemortem and postmortem digoxin levels, to learn if such differences can be related to the postmortem interval, to substantiate variation in postmortem blood values between samples taken from different sites, and finally to establish the most accurate way of estimating digoxin toxicity from postmortem specimens.

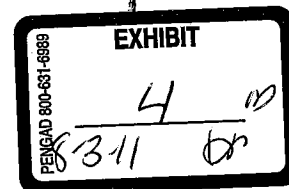
### Materials and Methods

Twenty-seven autopsy cases from two county hospitals were studied. Postmortem samples from the left ventricular cavity blood and vitreous humor were obtained in all cases. Sub-

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<sup>1</sup>Pathologist, Department of Anatomic and Clinical Pathology, St. Paul Ramsey Hospital, St. Paul, Minn. 55101.

<sup>2</sup>Chief of pathology, Hennepin County Medical Center, Minneapolis, Minn. and medical examiner, Hennepin County, Minneapolis, Minn. 55415.



clavian and femoral venous blood samples were obtained in 24 and 11 cases, respectively. All patients were receiving therapeutic doses of digoxin by various routes of administration for at least one week prior to death. No cases of suicidal or acute accidental poisoning were included. Antemortem serum samples were available for analysis in all cases, and the last digoxin dose was administered a minimum of 4 h before an antemortem sample was obtained. The blood urea nitrogen and interval between death and postmortem sampling (postmortem interval) were recorded.

Samples were centrifuged immediately, and the serum was refrigerated at 4 °C. Assays were performed within 72 h. In one hospital (St. Paul-Ramsey) assays were performed with material from Corning Medical Diagnostics, while in the second institution (HCMC) the materials used were from New England Nuclear. The procedure in either case was based on the principles of Smith et al [1] and involved the competitive binding of <sup>125</sup>I-labeled digoxin and unlabeled digoxin (present in the serum or vitreous sample) with a specific rabbit anti-digoxin antibody. The digoxin bound to antibody was separated by absorbing out the unbound digoxin (both labeled and unlabeled) with charcoal. In the Corning procedure this step was omitted because the antibody was precoated to glass beads. The bound fraction was counted with a gamma scintillation counter, and the percentage of bound <sup>125</sup>I-labeled digoxin was calculated. The digoxin level in the sample was determined from a standard curve, constructed daily by using five standards. Corning and New England Nuclear standards ranged from 0 to 5.0 ng/ml and 0.5 to 8 ng/ml, respectively. There was no difficulty in performing the postmortem tests with either procedure. The results were both internally consistent and showed good correlation between the two institutions when analyzed statistically.

The time from antemortem sampling to death ranged from 1 to 48 h, with a mean of 7.7 h. It was therefore necessary to correct for continued metabolism of the drug during the interval between the antemortem sample and death by determining the drug half-life in each case. Approximately 90% of digoxin was excreted unchanged by the kidney, and the half-life was therefore related to renal function. Each patient had a blood urea nitrogen (BUN) test performed within one day of death, and drug half-lives were determined by using data published by Jelliffe [13]. The immediate antemortem digoxin level was then calculated by using the formula

$$\ln N_t = \ln N_0 - \ln 2(t/T_{1/2})$$

where

$N_t$  = serum digoxin level at time of death,

$N_0$  = serum digoxin level at time of antemortem sampling,

$t$  = time interval between drawing of antemortem sample and death, and

$T_{1/2}$  = digoxin half-life based on BUN [13].

## Results

Postmortem intervals ranged from 1.0 to 22.4 h, with a mean of 10.8 h. Compared to antemortem levels, average postmortem serum digoxin levels were significantly higher ( $P < 0.001$ ) in samples taken from the heart, subclavian vein, and femoral vein (Table 1). Postmortem cardiac serum levels exceeded antemortem levels in all 26 cases where the postmortem interval was greater than an hour, and in no case did the postmortem level fall below the antemortem values on samples from heart or subclavian vein. In contrast, 2 of the 11 cases in which femoral samples were drawn had lower postmortem serum values than the corresponding antemortem levels (Cases 1 and 26). The mean of postmortem to antemortem ratios was 1.96 for heart, 1.63 for subclavian, and 1.42 for femoral samples. Vitreous levels were somewhat more variable, with 23 falling below, 3 exceeding, and 1 equaling antemortem levels. The mean ratio of vitreous to antemortem values was 0.71.

TABLE 1—Comparison of antemortem and postmortem serum digoxin levels.

Serum Digoxin Levels, ng/ml<sup>a</sup>

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TABLE 1—Comparison of antemortem and postmortem serum digoxin levels.

Case	BUN, <sup>a</sup> mg/dl	Serum Digoxin Levels, ng/ml <sup>b</sup>				
		Antemortem		Postmortem		
		At Time of Sampling	Calculated for Time of Death	Heart	Subclavian	Femoral
						Vitreous
1	24	17.3	15.8	25.8	18.2	15.2
2	27	8.2	8.0	9.8	9.2	2.4
3	122	6.6	6.6	8.8	8.4	4.2
4	59	5.1	4.8	9.4	9.8	3.8
5	44	4.5	4.0	7.8	7.5	3.8
6	70	4.0	3.8	7.9	7.9	2.1
7	100	3.5	3.4	5.7	5.6	2.1
8	87	3.3	3.2	4.2	3.8	1.5
9	94	2.7	2.7	2.7	3.0	1.4
10	41	3.0	2.4	5.2	4.4	2.0
11	14	2.7	2.2	4.5	4.2	2.1
12	150	2.1	2.0	5.4	3.2	2.4
13	30	2.3	2.0	3.5	3.1	1.5
14	20	2.0	1.9	4.7	3.1	1.4
15	22	1.8	1.8	5.0	...	1.8
16	78	1.9	1.6	2.2	2.0	0.6
17	28	1.9	1.6	4.8	...	1.3
18	75	1.7	1.6	2.0	1.8	1.1
19	56	1.6	1.4	3.5	2.6	0.5
20	90	1.5	1.4	3.2	2.1	0.6
21	16	1.5	1.4	2.5	2.2	0.7
22	40	1.4	1.3	1.7	1.3	0.7
23	14	1.2	1.2	2.3	1.6	0.4
24	22	1.4	1.2	2.7	2.3	1.0
25	56	1.8	1.0	2.9	2.5	1.1
26	32	0.6	0.6	1.2	0.9	0.4
27	20	0.5	0.3	0.8	0.9	0.5

<sup>a</sup>All urea nitrogen values were obtained from blood specimens drawn less than 24 h before death.<sup>b</sup>All cases in which a femoral specimen was obtained were from one institution (HCMC) and the materials for assay were supplied by New England Nuclear. The remaining tests were performed in the second hospital with assay material from: Corning Medical Diagnostics.

No useful correlation could be made between postmortem interval and either the absolute or relative change in postmortem samples, regardless of the site of sampling (Table 2). Case 9 had the shortest postmortem interval and the least amount of change; however, this trend did not hold true for a major portion of the cases. Case 17 showed the greatest relative increase in heart level with a postmortem interval in the mid-range, while Case 2, with a much longer postmortem interval, showed the second lowest change of the series.

If a diagnosis of digoxin toxicity were to be made on the basis of serum levels equal to or greater than 2 ng/ml, 48% of patients in this series would have been so diagnosed with the immediate antemortem value. With the postmortem heart samples, the figure would rise to 89%. Similarly, subclavian and femoral samples also lack specificity for digoxin toxicity. However, a postmortem serum level below 2 ng/ml does appear to be strong evidence against toxic levels in the antemortem stage.

Although the vitreous concentrations also differed markedly from true antemortem concentrations, they were more accurate indicators of toxicity. Ten patients (37%) had vitreous levels equaling or exceeding 2.0 ng/ml. Each of these ten cases also had a toxic antemortem serum level. Only three cases of possible toxicity (based on elevated antemortem levels) were not detected by vitreous determinations.

TABLE 2--Ratio of postmortem to antemortem digoxin levels and relationship to postmortem interval (PMI).

Case	PMI, h	Postmortem to Antemortem Ratio			
		Heart	Subclavian	Femoral	Vitreous
1	17.0	1.63	1.15	0.96	0.67
2	15.2	1.22	1.15	...	0.30
3	5.7	1.33	1.27	...	0.64
4	19.0	1.96	2.04	1.56	0.79
5	13.0	1.95	1.88	1.40	0.95
6	21.0	1.84	2.08	...	0.55
7	20.9	1.68	1.65	...	0.62
8	4.0	1.31	1.18	...	0.47
9	1.0	1.00	1.11	...	0.52
10	13.5	2.17	1.83	1.29	0.83
11	10.8	2.04	1.91	1.59	0.95
12	16.3	2.70	1.60	...	1.20
13	6.5	1.75	...	...	0.75
14	16.2	2.47	1.63	1.52	0.74
15	14.0	2.78	...	...	1.00
16	22.4	1.38	1.25	...	0.38
17	11.3	3.00	...	...	0.81
18	4.4	1.25	1.12	...	0.69
19	15.0	2.50	1.86	...	0.36
20	10.8	2.28	1.50	...	0.43
21	3.5	1.78	1.57	1.43	0.50
22	2.5	1.31	1.00	...	0.54
23	3.8	1.92	1.33	1.08	0.33
24	3.4	2.24	1.42	1.83	0.83
25	3.0	2.90	2.50	2.30	1.10
26	16.0	2.00	1.50	0.67	0.67
27	6.8	2.67	3.00	...	1.67
Mean	10.6 ± 6.25	1.96 ± 0.56	1.63 ± 0.48	1.42 ± 0.44	0.71 ± 0.30
Correlation with PMI, r	...	0.15	0.14	0.48	-0.06

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### Discussion

It is clear from this investigation that postmortem digoxin levels taken from cardiac blood, venous blood, or vitreous humor do not mirror the antemortem levels. Substantial increases in serum levels occur following death, irrespective of the source of the sample. It seems probable that a new drug equilibrium between blood and tissue is established after death. Several investigators have found various tissue levels to exceed blood levels, with the highest concentrations occurring in the heart and kidney [8,9,14]. The ratio of myocardial to serum concentrations is approximately 30:1. With cell death and subsequent loss of membrane integrity, digoxin must diffuse from tissue into the adjacent circulatory compartment. As a consequence it is possible to falsely diagnose digoxin toxicity from postmortem serum specimens no matter what the source of the samples, but a postmortem serum level below 2 ng/ml will exclude the presence of toxic levels in the antemortem state.

Conversely, vitreous levels are usually below the true antemortem values. The vitreous compartment appears to be less permeable to compounds in the circulation. DiMaio et al [6] have suggested that vitreous to serum ratios less than one reflect rising blood levels at the time of death and those greater than one reflect falling levels. Our data do not support such a concept. All patients died between 6 and 120 h after their last dose. Since the time required for equilibration with blood and myocardium is usually less than 4 h after oral administration, blood levels should have been falling in every case. It is possible that in most individuals vitreous levels never equilibrate with blood. However, this series does establish that significantly elevated vitreous levels correspond with toxic antemortem serum levels.

A larger series correlating true antemortem with postmortem concentrations might establish a serum or vitreous threshold concentration that most accurately reflects the clinical situation. In the absence of such a threshold concentration for guidance, we think that a combination of venous serum and vitreous humor values provide the most useful information. Femoral samples appear preferable to subclavian.

A striking finding of this study is that 14 of 27, or 52%, of the patients had toxic levels at the time the antemortem samples were drawn, most of which were obtained for electrolyte or cardiac enzyme determination. Digoxin toxicity was thought to be the cause of death in Case 1 and may well have been a contributory factor in the deaths of Cases 2, 3, and 4. We have found this type of retrospective analysis useful and strongly recommend saving serum for five to seven days in the laboratory. The cardiac glycoside dosage is frequently not adjusted for acute renal failure or renal hypoperfusion commonly seen in severely ill patients.

This investigation also raises suspicion regarding many studies in postmortem toxicology. If indeed a new blood-tissue equilibrium is established with digoxin after death, a similar situation may exist for many compounds studied during autopsy. Gee [15] has already reported varying barbiturate levels between cardiac and femoral vein specimens, with differences as high as 6.0 mg/100 ml. Other drugs whose postmortem distribution through the vascular system is more uniform than barbiturate might show significant variations between specimens drawn during life and after death.

### Summary

Postmortem serum digoxin levels from any source routinely exceed antemortem values. Variation resulting from site of sampling gave a mean postmortem to antemortem ratio of 1.96 for heart, 1.63 for subclavian vein, and 1.42 for femoral vein samples.

No correlation could be made between the postmortem interval and the increase in postmortem serum values, irrespective of the site of sampling.

A combination of femoral venous serum and vitreous humor values gave the best information for determining possible antemortem digoxin toxicity.

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Deposition

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## References

- [1] Smith, T. W., Butler, V. P., and Haber, E., "Determination of Therapeutic and Toxic Serum Digoxin Concentrations by Radioimmunoassay," *The New England Journal of Medicine*, Vol. 281, 1969, pp. 1212-1216.
- [2] Smith, T. W. and Haber, E., "Digoxin Intoxication: The Relationship of Clinical Presentation to Serum Digoxin Concentration," *The Journal of Clinical Investigation*, Vol. 49, 1970, pp. 2377-2386.
- [3] Park, H. M., Chem, I., Manittas, G. T., Lowey, A., and Saenger, E. L., "Clinical Evaluation of Radioimmunoassay of Digoxin," *Journal of Nuclear Medicine*, Vol. 14, 1973, pp. 531-533.
- [4] Beller, G. A., Smith, T. W., Abelman, W. H., Huber, E., and Hood, W. B., "Digitalis Intoxication: A Prospective Clinical Study with Serum Level Correlations," *The New England Journal of Medicine*, Vol. 284, 1971, pp. 980-997.
- [5] Moffat, A. C., "Interpretation of Postmortem Serum Levels of Cardiac Glycosides After Suspected Overdosage," *Acta Pharmacologica et Toxicologica*, Vol. 35, 1974, pp. 386-394.
- [6] DiMaio, V. J. M., Garriott, J. C., and Putnam, R., "Digoxin Concentrations in Postmortem Specimens After Overdose and Therapeutic Use," *Journal of Forensic Science*, Vol. 20, No. 2, April 1975, pp. 340-347.
- [7] Phillips, A. P., "Case Experience with Digoxin Analysis of Postmortem Blood," *Journal of the Forensic Science Society*, Vol. 14, 1974, pp. 137-140.
- [8] Iisalo, E. and Nuutila, M., "Myocardial Digoxin Concentrations in Fatal Intoxications," *The Lancet*, 3 Feb. 1973, p. 257.
- [9] Karjalainen, J., Ojala, K., and Reissell, P., "Tissue Concentrations of Digoxin in an Autopsy Material," *Acta Pharmacologica et Toxicologica*, Vol. 34, 1974, pp. 385-390.
- [10] Selesky, M., Spiehler, V., Cravey, R. H., and Elliot, H. W., "Digoxin Concentrations in Fatal Cases," *Journal of Forensic Sciences*, Vol. 22, No. 2, April 1977, pp. 409-417.
- [11] Holt, D. W. and Benstead, J. G., "Postmortem Assay of Digoxin by Radioimmunoassay," *Journal of Clinical Pathology*, Vol. 28, 1975, pp. 483-486.
- [12] Dickson, S. J. and Blazey, N. D., "Postmortem Digoxin Levels--Two Unusual Case Reports," *Forensic Science*, Vol. 9, 1977, pp. 145-150.
- [13] Jelliffe, R. W., "An Improved Method of Digoxin Therapy," *Annals of Internal Medicine*, Vol. 69, 1968, pp. 703-717.
- [14] Doherty, J. E., Perkins, W. H., and Flanigan, W. T., "The Distribution and Concentration of Trinitiated Digoxin in Human Tissues," *Annals of Internal Medicine*, Vol. 66, 1967, pp. 116-124.
- [15] Gee, D. J., *The Poisoned Patient: The Role of the Laboratory*, Ciba Foundation Symposium 26 (new series), Elsevier Excerpta Medica, North-Holland, Associated Scientific Publishers, New York, 1974, p. 243.

Address requests for reprints or additional information to  
 John I. Coe, M.D.  
 Hennepin County Medical Examiner's Office  
 730 South 7th St.  
 Minneapolis, Minn. 55415

UNITED STATES DISTRICT COURT OF THE  
SOUTHERN DISTRICT OF WEST VIRGINIA  
CHARLESTON DIVISION

Kathy McCornack, et al.

**THIS DOCUMENT RELATES TO:**

Plaintiffs,

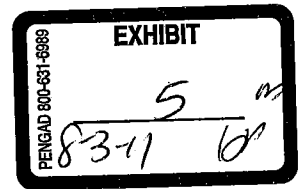
Case No.: 2:09-cv-0671

vs.

*Related MDL Case No.: 2:08-md-1968*

Actavis Totowa, LLC, et al.

Defendants.



**AMENDED NOTICE TO TAKE VIDEOTAPED ORAL DEPOSITION AND REQUEST  
FOR PRODUCTION AND COPYING OF DOCUMENTS AT THE DEPOSITION**

TO ALL PARTIES AND TO THEIR ATTORNEYS OF RECORD:

**PLEASE TAKE NOTICE** that, under Federal Rules of Civil Procedure 26(d), 30 and 45, Plaintiffs will take the deposition of **DR. WILLIAM L. GALANTER** on **Wednesday, August 3, 2011 at 10:00 a.m.** at MJ Reporting, 10 North Martingale Road, Schaumburg, IL 60173, (847) 619-7155.

The oral examination will continue from day to day until completed. This deposition will be recorded stenographically, may be recorded on videotape and will comply with any relevant orders in this litigation, including Pretrial Order No. 22, attached hereto as Exhibit A. This deposition is noticed in the above-captioned matter for any and all purposes permitted by the Federal Rules of Civil Procedure and any other federal, state, or local rules that apply to this action and the deposition will be taken in accordance with these rules. A copy of the subpoena duces tecum to appear and testify at a hearing or trial in a civil case is attached hereto as Exhibit

B and served herewith. Pursuant to Federal Rule of Civil Procedure 30(b)(2) and 45(a), Plaintiffs request that Dr. Galanter produce for inspection at the time of deposition:

1. The witness' current curriculum vitae or resume.
2. All correspondence and communication between the witness or anyone acting on the witness' behalf, and attorneys representing defendants in this and the MDL Digitek® litigation.
3. All other documents prepared by the attorneys for the defendants and sent to the witness.
4. All documents, including documents and deposition transcripts which refer or relate to this and the MDL Digitek® litigation that the witness received from any source.
5. All retainer agreements or other agreements under which the witness has been or will be paid for work related to this and the related MDL Digitek® litigation.
6. All bills that the witness has rendered to attorneys and law firms in connection with this and the MDL Digitek® litigation.
7. A copy of the witness' entire file, including all electronic documents, and correspondence, in connection with this and the MDL Digitek® litigation.
8. All documents, including additional materials received or reviewed, tangible things, data, or writings that relied upon, examined, considered, or rejected in preparing the reports in this and the MDL Digitek® litigation, or subsequent to preparing his report.
9. Everything the witness reviewed that indicates any person may have ingested defective Digitek®.

10. All notes that the witness has taken in connection with review of this and the MDL Digitek® litigation matters.
11. All documents that the witness has prepared concerning the subject matter of this and the MDL Digitek® litigation.
12. All medical, scientific or other literature on which the witness relies in connection with the opinions expressed in his expert report.
13. All documents, tangible things, data, or writings concerning whether a Digitek® tablet that may have been adulterated may have ever been received by a pharmacist or consumer. This request is not limited to just the Digitek® tablets recalled in 2008 by Defendant Actavis, but to all Digitek® tablets that may have ever been received by a pharmacist or consumer and suspected to be adulterated for any reason.
14. All documents the witness reviewed in preparation for this deposition.

Respectfully Submitted:

Dated: July 28, 2011

/s/ Terry Kilpatrick  
Terry Kilpatrick (Calif. Bar No. 163197)  
Attorneys for Plaintiffs  
Ernst Law Group  
1020 Palm Street  
San Luis Obispo, CA. 93401  
Tel: 805-541-0300  
Fax: 805-541-5168  
E-mail: tk@ernstlawgroup.com

**CERTIFICATE OF SERVICE**

I hereby certify that on July 28, 2011, I or an employee under my control electronically filed the foregoing document with the Clerk of Court using the CM/ECF system, which will send notification of such filing to all counsel of record.

Dated: July 28, 2011

/s/ Terry Kilpatrick  
Terry Kilpatrick (Calif. Bar No. 163197)  
Attorneys for Plaintiffs  
Ernst Law Group  
1020 Palm Street  
San Luis Obispo, CA. 93401  
Tel: 805-541-0300  
Fax: 805-541-5168  
E-mail: tk@ernstlawgroup.com

# EXHIBIT A

IN THE UNITED STATES DISTRICT COURT  
FOR THE SOUTHERN DISTRICT OF WEST VIRGINIA  
CHARLESTON DIVISION

IN RE DIGITEK®  
PRODUCT LIABILITY LITIGATION

MDL NO. 1968

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THIS DOCUMENT RELATES TO ALL CASES

PRETRIAL ORDER #22  
(Conduct of Discovery)

INTRODUCTION

A. Coordination with Other Litigation

1. Coordination to Extent Practicable

Plaintiffs and Defendants in this litigation, and in particular the Plaintiffs' Liaison Counsel, PSC, Defendants' Liaison Counsel, and all other counsel designated by the Court in prior or subsequent Pretrial Orders, shall work to coordinate to the extent practicable the conduct of this litigation with other product liability or marketing or sales practices actions involving Digitek® pending in any State Court. Such coordination is intended to conserve scarce judicial resources, eliminate duplicative discovery, serve the convenience of the parties and witnesses, and promote the just and efficient conduct of this litigation. It is contemplated by the Court and the parties that all discovery conducted in these proceedings may be utilized in any related State Court action, in accordance with the State's law and rules of evidence, and vice versa, subject to an appropriate cost-sharing provision which will be the subject of a further order. All discovery obtained in these proceedings which is used in any State Court litigation is subject to this Order, any protective order(s) entered by this Court, and such future cost-sharing orders as may be entered.

2. Intent to Coordinate with State Courts

In order to achieve the full benefits of this MDL proceeding, this Court intends to coordinate with State Courts presiding over related cases, to the extent that such State Courts so desire, such as through joint orders that will allow the parties in the State Court actions to fully utilize any discovery conducted in the MDL proceedings and vice versa. As the Court indicated at the initial case management conference, this Court intends to work actively to reach out to any State Court that is interested in coordinating discovery activities. The Court expects that counsel for parties in the MDL proceeding will help ensure that such coordination is achieved where it is practicable.

B. Production of Documents

1. Depository

The PSC shall bear the cost of and administer its own depository. All documents produced by Defendants in this proceeding shall be produced to the PSC's designee. The PSC shall make the documents produced by Defendants available to Plaintiffs in State Court litigation subject to an appropriate cost-sharing provision which will be the subject of a further order. This production shall not preclude any party from asserting in any action that such documents are inadmissible at trial, nor shall this provision be construed to supersede or amend any State's law or State Court's rules pertaining to such documents.

2. Use of On-Line Document Depositories

Counsel shall take all reasonable and necessary steps to assure the security of any confidential information produced pursuant to the Protective Order issued by this Court and will limit access to confidential information to those persons covered by the Protective Order. In particular, if counsel for any party makes documents available via the Internet, such counsel shall take all reasonable and necessary steps to ensure that the Internet site is secure and may not be

accessed by individuals who are not authorized to review confidential information.

3. Effect on Document Production

This Order shall be read in conjunction with other Pre-trial Orders of this Court that reference production of documents, as well as the Federal Rules of Civil Procedure, and the Federal Rules of Evidence; nothing contained herein shall limit or abridge the parties rights or prerogatives under such orders and rules.

Upon request by any party supplying confidential information, any party using an Internet site must certify to the Court and the supplying party that the Internet site is secure and may only be accessed pursuant to the Protective Order entered by this Court. In the event the Internet site is made available to persons outside the MDL, they will be governed by appropriate further orders of this Court or appropriate state courts.

**DEPOSITION GUIDELINES**

C. Deposition Notices

1. This Order applies to all depositions in MDL-1968, which will be noticed and conducted pursuant to Fed. R. Civ. P. 30 and this Order.

2. This Order, in its entirety, shall be attached to any non-party subpoena or deposition notice.

3. Each deposition notice shall include the name and, if known, the general occupational description of each deponent, and the date, time and place of the deposition.

4. In order for counsel to make arrangements for adequate deposition space, whenever feasible, counsel who intend to attend a deposition noticed by MDL-1968 plaintiffs should provide notice to Plaintiffs' Liaison Counsel of their intention to attend. Counsel who intend to attend a deposition noticed by the MDL-1968 defendants should send notice of their

intention to Defendants' Liaison Counsel. As to all parties, notice of intention to attend shall be provided within one week of the deposition date.

5. Deposition notices shall state whether the deposition is to be videotaped and, if so, the name, firm and address of the videotape recorders. All videotape depositions shall proceed pursuant to the provisions of section L, *infra*.

D. Avoidance of Duplicative Depositions

As a general rule, absent good cause or the agreement of the parties, no witness should be deposed on the same subject more than once in these proceedings. Defendants' Liaison Counsel shall advise the PSC of all depositions that have been taken by Plaintiffs in other litigation related to Digitek® and shall provide the transcripts of such depositions to the PSC.

E. Cooperation

Witnesses, parties and counsel must conduct themselves at depositions in a temperate, dignified, and responsible manner. Opposing counsel and the deponent must be treated with civility and respect. There shall be no smoking or use of other tobacco products in any room in which a deposition is being conducted, including before, during or after a deposition, or in the deposition room during deposition recesses.

F. Scheduling

Absent extraordinary circumstances, counsel shall consult in advance with opposing counsel and proposed deponents in an effort to schedule depositions at mutually convenient times and locations. Counsel are expected to cooperate and coordinate the scheduling of depositions. Only one deposition of a current or former employee of the defendants shall be taken per day until such time as there is a demonstrated need to multitrack depositions of the employees of the defendants. At that time the parties shall meet and confer on the establishment of a reasonable schedule for the multi-tracking of depositions of employees of the defendants.

For depositions which are not case specific, each side shall be notified at least thirty (30) days in advance of a deposition, absent agreement by parties, time constraints due to PTO # 16 or by leave of Court. Given time limits contained in the Case Management and Scheduling Order, PTO # 16, Defendants agree to make deponents, such as employees or former employees, available for deposition at such times and places so as to permit compliance with deadlines contained in PTO # 16.

No depositions shall be scheduled on secular or religious holidays.

G. Cross-Notices Between State Court Cases and These Proceedings

In order to avoid duplicative discovery and to prevent the unnecessary expenditure of judicial resources and the resources of the parties, steps should be taken to encourage counsel in related state court proceedings to coordinate their depositions with MDL-1968 depositions. Depositions originally noticed in this MDL may be cross-noticed in appropriate state court cases by Plaintiffs' counsel or Defendants' counsel. Depositions originally noticed in state court cases may be cross-noticed in this MDL by Plaintiffs' counsel or Defendants' counsel. Such cross-notices shall be issued at least fifteen (15) days in advance of the deposition or in accordance with local rules.

If counsel cannot agree on the order of questioning at a deposition, these rules shall apply: if the deposition was originally noticed in this MDL, whether or not later cross-noticed in state court proceedings, MDL counsel shall go first in the deposition.

Nothing in this provision shall be construed as an injunctive or equitable order affecting state court proceedings. Rather, this provision is intended to reflect this Court's desire for voluntary state-federal coordination.

H. Postponements

Once a deposition has been scheduled, it shall not be taken off calendar, postponed,

rescheduled, or relocated less than five (5) calendar days in advance of the date it is scheduled to occur, except upon agreement of counsel or by leave of Court for good cause.

I. Deposition Length and Day

A deposition day shall begin as early as practicable and shall terminate no later than 5:30 p.m. (except Friday when depositions shall end no later than 1:00 p.m.), local time. All parties shall work together and in good faith to make reasonable exceptions to the length of the deposition day as necessary.

A deposition shall last no longer than fourteen (14) hours total examination time, except upon agreement of counsel or by leave of Court. This time includes examinations performed by all parties and does not include regular and reasonable breaks taken during the deposition.

J. Continuance of Deposition

If a deposition is not concluded during the time allotted in the deposition notice, and time still remains for the examining party under subsection I, then the deposition shall be continued on a newly-noticed date or an agreed date. In such circumstances, a ten (10) day notice will be sufficient to notice a continued deposition.

K. Locations for Taking Depositions

1. The parties will work together to cooperate in the location and circumstances of all scheduled depositions.

2. Unless otherwise agreed, depositions of plaintiffs will take place in each plaintiff's home district.

3. Unless otherwise agreed by the parties prior to the noticing of an expert, treating physician and/or prescribing physician deposition, the deposition of such witness shall take place in the home district of the witness.

4. The location of the deposition shall be as consistent as possible within each city, so that videotape equipment, if being used, can be left in place.

5. To the extent reasonably possible, depositions of current and former employees of defendants will take place in the district of such employee's place of business. Defense counsel will make reasonable efforts to obtain the agreement of former employees of defendants to appear at the same location as current employees of the same defendant. Absent such agreement, that deposition will take place either within the federal district in which the former employee resides or at a location mutually agreeable to the former employee and parties.

6. Unless otherwise provided by law or court order, attorneys attending and participating in a deposition are not required to be licensed to practice law in the state in which the deposition is being taken.

L. Attendance

Unless otherwise agreed to by the parties, depositions may be attended only by the parties, the deponent, the deponent's attorney, the examining attorneys, attorneys of record in MDL-1968 or state cases, in-house counsel for the parties, court reporters, videographers, and any person who is assisting in the litigation and whose presence is reasonably required by counsel. Experts who have signed the Protective Order may attend expert depositions of the other parties' experts but may not participate in the depositions. Upon application, and for good cause shown, the Court may permit attendance by a person who does not fall within any of the categories set forth in the previous sentence. While a deponent is being examined about any document that the parties have agreed is confidential, or the Court has determined to be confidential, attendance at that portion of the deposition by persons to whom disclosure is not authorized by agreement of the parties or by order of the Court shall be prohibited. Any portion

of the deposition transcript containing documents or information subject to the Protective Order entered in this case shall be sealed in accordance with the terms of the Protective Order.

Unnecessary attendance by counsel is discouraged and may not be compensated in any fee application to the Court.

Telephonic participation shall be addressed on a witness by witness basis.

M. Conduct

Except by order of the Court, the following shall apply at all depositions:

1. Examination

Each side should ordinarily designate no more than two attorneys for the MDL. For state cases, one plaintiff attorney for each state case or state consolidation shall be designated to participate in the deposition and conduct non-duplicative questioning.

In some depositions, there may be sufficient divergence of positions among various parties such that additional examiners may be appropriate on non-redundant matters. Therefore, other attorneys will be permitted to examine deponents on non-redundant matters. Further, even if there is no divergence of position, if a state court attorney has non-redundant questioning he or she deems necessary or appropriate, further questioning by that state court lawyer may proceed, subject to overall time limits.

When a party believes that it may be necessary to examine the deponent on non-redundant matters due to a divergence of interest, such party shall designate one attorney to conduct such non-redundant examination after the initial examination has concluded.

Counsel should cooperate in the allocation of time in order to comply with the time limits set by the Court.

2. Objections and Directions Not to Answer

Unless otherwise agreed by the parties, and noted on the record, the following

stipulations shall apply to all discovery depositions in this action:

- a) Objections must be limited to (1) those that would be waived if not made pursuant to Fed. R. Civ. P. 32(d)(3); and (2) those necessary to assert a privilege, enforce a limitation on evidence directed by the Court or present a motion under Fed. R. Civ. P. 30(d)(3). No other objections can be raised during the course of the deposition. In the event privilege is claimed, examining counsel may make appropriate inquiry about the basis for asserting privilege.
- b) Speaking objections that refer to the facts of the case or suggest an answer to the deponent are improper and must not be made in the presence of the deponent.
- c) Asking redundant, repetitive, multiple asked-and-answered questions in an effort to alter or amend a deponent's testimony is improper and must not be done in the deponent's presence.

3. Objections to Documents

Objections as to the relevance of documents are not waived, and are reserved for later ruling by the Court or by the trial judge. No objections to the use of any document are necessary.

4. Disputes During Depositions

Disputes arising during depositions that cannot be resolved by agreement and that, if not immediately resolved, will significantly disrupt the discovery schedule or require rescheduling of the deposition, or might result in the need to conduct a supplemental deposition, shall be presented to Judge Goodwin or Magistrate Judge Stanley by telephone. In the event both Judge

Goodwin and Magistrate Judge Stanley are not available, the deposition shall continue with full reservation of rights of the interrogation for a ruling at the earliest possible time.

If the nature of the dispute would not stop the deposition from going forward, the parties may elect to either present the matter to Judge Goodwin or Magistrate Judge Stanley by telephone, or to present the dispute to the Court in writing. If the parties elect to present the dispute to the Court in writing, each side must submit a one (1) page summary of its position and any authority relevant to the dispute. The Court will issue a prompt ruling, as its schedule permits.

In the event the Court is unavailable by telephone to resolve disputes arising during the course of a deposition, the deposition shall nevertheless continue to be taken as to matters not in dispute.

None of the provisions in this Section shall deny counsel the right to continue the deposition, file an appropriate motion with the Court at the conclusion of the deposition, and appear personally before the Court if counsel deems it necessary.

Disputes between the parties should be addressed to this Court rather than to the District Court in which the deposition is being conducted.

N. Stenographic Recording

A certified court reporter shall stenographically record all deposition proceedings and testimony. The court reporter shall administer the oath or affirmation to the deponent. A written transcript by the court reporter shall constitute the official record of the deposition for purposes of Fed. R. Civ. P. 30(e) (submission to the witness) and 30(f) (filing, exhibits). A copy of all deposition exhibits shall be included with the original deposition transcript.

Before commencement of the deposition, each witness, attorney, and any other person attending the deposition shall submit to the court reporter in writing his or her name, the name of

his or her firm, business address, and the name of the client he or she represents. The list of these people shall be included at the beginning of the deposition transcript.

O. Videotaped Depositions

The provisions of this Order regarding examination of deponents apply to videotaped depositions. Any deposition may be videotaped at the request of any party pursuant to the following terms and conditions:

1. Simultaneous Stenographic Recording

All videotaped depositions shall be simultaneously stenographically recorded in accordance with paragraph N, above.

2. Cost of the Deposition

The party requesting videotaping of the deposition shall bear the expense of the videotaping. Requests for the taxation of these costs and expenses may be made at the conclusion of the litigation in accordance with applicable law.

3. Videotape Operator

The operator(s) of the videotape recording equipment shall be subject to the provisions of Fed. R. Civ. P. 28(c). At the commencement of the deposition, the operator(s) shall swear or affirm to record the proceedings fairly and accurately.

4. Attendance

At the commencement of the deposition, each witness, attorney and any other person attending the deposition shall be identified on camera

5. Interruptions

No attorney or party shall direct instructions to the video operator as to the method of operating the equipment. The video camera operation will be suspended during the deposition only upon stipulation by counsel and "off the record" discussions. The video operator shall

record on camera the time of suspension and any subsequent reconvening of the deposition.

6. Standards

The deposition will be conducted in a manner to replicate, to the extent feasible, the presentation of evidence at trial. Unless physically incapacitated, the deponent shall be seated at a table except when reviewing or presenting demonstrative materials for which a change in position is needed. To the extent practicable, the deposition will be conducted in a neutral setting, against a solid background, with only such lighting as is required for accurate video recording. Lighting, camera angle, lens setting, and field of view will be changed only as necessary to record accurately the natural body movements of the deponent or to portray exhibits and materials used during the deposition.

The parties reserve the right to seek an Order from the Court that the examiner as well as the witness be recorded, and that if a second camera is necessary to accomplish such recording, such party agrees to bear such expense.

To the extent that technology permits, the parties reserve the right to format documents and other tangible materials so that a videotaped deponent who makes reference to such exhibits can be displayed contemporaneously with such exhibit.

7. Index

The videotape operator shall use a counter on the recording equipment and after completion of the deposition shall prepare a log, cross-referenced to counter numbers, that identifies the depositions on the tape at which examination by different counsel begins and ends, at which objections are made and examination resumes, at which exhibits are identified, and at which any interruption of continuous tape-recording occurs, whether for recesses, "off-the-record" discussions, mechanical failure, or otherwise.

8. Filing

After the deposition is completed, the video operator shall certify on camera the correctness, completeness, and accuracy of the videotape recording in the same manner as a stenographic Court reporter, and file a true copy of the videotape, the transcript, and certificate with Liaison Counsel for Plaintiffs and Defendants.

9. Technical Data

Technical data, such as recording speeds and other information needed to replay or copy the tape, shall be included on copies of the videotaped deposition.

P. Obtaining Copies of Transcripts and Videotapes

Any party may at its own expense obtain a copy of the videotape and the stenographic transcript by contacting the Liaison Counsel for the party noticing the deposition or the court reporter.

Q. Correction and Signing Depositions

A deponent will be given the opportunity to review their deposition and make corrections consistent with Federal Rule of Civil Procedure 30(e).

OTHER DISCOVERY

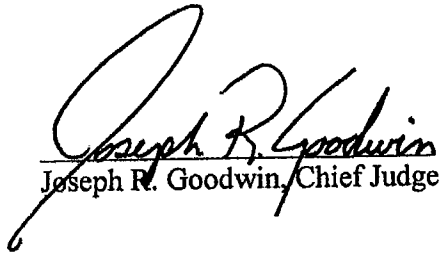
R. Effect on Other Discovery

With regard to other forms of discovery, including Interrogatories, Requests to Produce Documents, Requests to Admit and Right to Entry and Inspection, nothing contained herein shall limit or abridge the parties rights or prerogatives under previously entered orders of this Court, the Federal Rules of Civil Procedure and the Federal Rules of Evidence.

**IT IS SO ORDERED.**

The court **DIRECTS** the Clerk to file a copy of this order in 2-08-md-1968 which shall apply to each member Digitek-related case previously transferred to, removed to, or filed in this district, which includes counsel in all member cases up to and including civil action number 2-09-cv-0561. In cases subsequently filed in this district, a copy of the most recent pretrial order will be provided by the Clerk to counsel appearing in each new action at the time of filing of the complaint. In cases subsequently removed or transferred to this court, a copy of the most recent pretrial order will be provided by the Clerk to counsel appearing in each new action upon removal or transfer. It shall be the responsibility of the parties to review and abide by all pretrial orders previously entered by the court. The orders may be accessed through the CM/ECF system or the court's website at [www.wvsc.uscourts.gov](http://www.wvsc.uscourts.gov).

ENTER: May 19, 2009

  
Joseph R. Goodwin, Chief Judge

STIPULATED AND AGREED TO BY:

FOR DEFENDANTS:

s/ Matthew P. Moriarty  
RICHARD A. DEAN  
MATTHEW P. MORIARTY (WVSB #4571)  
TUCKER ELLIS & WEST LLP  
925 Euclid Avenue, Suite 1150  
Cleveland, Ohio 44115  
Tel: (216) 696-2137  
Fax: (216) 592-5009  
Richard.Dean@TuckerEllis.com  
Matthew.Moriarty@TuckerEllis.com  
Co-Lead Counsel for Actavis Defendants

s/ Harvey L. Kaplan  
HARVEY L. KAPLAN  
MADELEINE M. McDONOUGH  
SHOOK HARDY & BACON, L.L.P.  
2555 Grand Boulevard  
Kansas City, Missouri 64108  
Tel: (816) 559-2214  
Fax: (816) 421-5547  
hkaplan@shb.com  
mmcdonough@shb.com  
Co-Lead Counsel for Mylan Defendants

s/ Rebecca A. Betts  
REBECCA A. BETTS (WVSB #329)  
ALLEN GUTHRIE & THOMAS, PLLC  
500 Lee Street, East, Suite 800  
P.O. Box 3394  
Charleston, West Virginia 25333-3394  
Tel: (304) 345-7250  
Fax: (304) 345-9941  
rabetts@agmtlaw.com  
Liaison Counsel for Defendants

FOR PLAINTIFFS:

s/ Carl Frankovitch  
CARL N. FRANKOVITCH (WVSB # 4746)  
FRANKOVITCH, ANETAKIS, COLANTONIO &  
SIMON  
337 Penco Road  
Weirton, West Virginia 26062  
Tel: (304) 723-4400  
Fax: (304) 723-5892  
carln@facslaw.com  
Co-Lead Counsel for Plaintiffs

s/ Harry F. Bell, Jr.  
HARRY F. BELL, JR. (WVSB #297)  
BELL & BANDS PLLC  
300 Capitol Street  
P.O. Box 1723  
Charleston, West Virginia 25326-1723  
Tel: (304) 345-1700  
Fax: (304) 345-1715  
hfbell@belllaw.com  
Co-Lead and Liaison Counsel for Plaintiffs

s/ Fred Thompson, III  
FRED THOMPSON, III  
MOTLEY RICE LLC  
28 Bridgeside Blvd.  
P.O. Box 1792  
Mt. Pleasant, South Carolina 29465  
Tel: (843) 216-9000  
Fax: (843) 216-9450  
fthompson@motleyrice.com  
Co-Lead and Liaison Counsel for Plaintiffs

# EXHIBIT B

AO 88A (Rev. 06/09) Subpoena to Testify at a Deposition in a Civil Action

UNITED STATES DISTRICT COURT

for the

N.D. of Illinois, Eastern Division

Kathy McCornack, et al.

*Plaintiff*

v.

Actavis Totowa, LLC, et al.

*Defendant*

Civil Action No. 2:09-cv-0671

(If the action is pending in another district, state where:

Southern District of West Virginia )

SUBPOENA TO TESTIFY AT A DEPOSITION IN A CIVIL ACTION

To: Dr. William L. Galanter, 940 S. Wood, MC 718, Chicago, IL 60612

☒ **Testimony:** YOU ARE COMMANDED to appear at the time, date, and place set forth below to testify at a deposition to be taken in this civil action. If you are an organization that is *not* a party in this case, you must designate one or more officers, directors, or managing agents, or designate other persons who consent to testify on your behalf about the following matters, or those set forth in an attachment:

Place: MJ Reporting  
10 North Martingale Road  
Schaumburg, IL 60173 (847) 619-7155

Date and Time:  
08/03/2011 10:00 am

The deposition will be recorded by this method: Stenographically and may be recorded by videotape

☒ **Production:** You, or your representatives, must also bring with you to the deposition the following documents, electronically stored information, or objects, and permit their inspection, copying, testing, or sampling of the material:

The items listed as 1 - 14 at the end of the attached Notice of Deposition.

The provisions of Fed. R. Civ. P. 45(c), relating to your protection as a person subject to a subpoena, and Rule 45 (d) and (e), relating to your duty to respond to this subpoena and the potential consequences of not doing so, are attached.

Date: 07/28/2011

CLERK OF COURT

OR

*Signature of Clerk or Deputy Clerk*

*Attorney's signature*

The name, address, e-mail, and telephone number of the attorney representing (name of party) Plaintiffs, KATHY McCORNACK, et al., who issues or requests this subpoena, are:

Terry Kilpatrick, ERNST LAW GROUP, 1020 Palm Street, San Luis Obispo, CA 93401, tk@ernstlawgroup.com, (805) 541-0300

AO 88A (Rev. 06/09) Subpoena to Testify at a Deposition in a Civil Action (Page 2)

Civil Action No. 2:09-cv-0671

**PROOF OF SERVICE**

*(This section should not be filed with the court unless required by Fed. R. Civ. P. 45.)*

This subpoena for *(name of individual and title, if any)* \_\_\_\_\_  
was received by me on *(date)* \_\_\_\_\_.

☐ I served the subpoena by delivering a copy to the named individual as follows: \_\_\_\_\_

\_\_\_\_\_ on *(date)* \_\_\_\_\_; or

☐ I returned the subpoena unexecuted because: \_\_\_\_\_

Unless the subpoena was issued on behalf of the United States, or one of its officers or agents, I have also  
tendered to the witness fees for one day's attendance, and the mileage allowed by law, in the amount of  
\$ \_\_\_\_\_.

My fees are \$ \_\_\_\_\_ for travel and \$ \_\_\_\_\_ for services, for a total of \$ 0.00.

I declare under penalty of perjury that this information is true.

Date: \_\_\_\_\_

\_\_\_\_\_  
*Server's signature*

\_\_\_\_\_  
*Printed name and title*

\_\_\_\_\_  
*Server's address*

Additional information regarding attempted service, etc:

**Federal Rule of Civil Procedure 45 (c), (d), and (e) (Effective 12/1/07)**

**(c) Protecting a Person Subject to a Subpoena.**

(1) *Avoiding Undue Burden or Expense; Sanctions.* A party or attorney responsible for issuing and serving a subpoena must take reasonable steps to avoid imposing undue burden or expense on a person subject to the subpoena. The issuing court must enforce this duty and impose an appropriate sanction — which may include lost earnings and reasonable attorney's fees — on a party or attorney who fails to comply.

(2) *Command to Produce Materials or Permit Inspection.*

(A) *Appearance Not Required.* A person commanded to produce documents, electronically stored information, or tangible things, or to permit the inspection of premises, need not appear in person at the place of production or inspection unless also commanded to appear for a deposition, hearing, or trial.

(B) *Objections.* A person commanded to produce documents or tangible things or to permit inspection may serve on the party or attorney designated in the subpoena a written objection to inspecting, copying, testing or sampling any or all of the materials or to inspecting the premises — or to producing electronically stored information in the form or forms requested. The objection must be served before the earlier of the time specified for compliance or 14 days after the subpoena is served. If an objection is made, the following rules apply:

(i) At any time, on notice to the commanded person, the serving party may move the issuing court for an order compelling production or inspection.

(ii) These acts may be required only as directed in the order, and the order must protect a person who is neither a party nor a party's officer from significant expense resulting from compliance.

(3) *Quashing or Modifying a Subpoena.*

(A) *When Required.* On timely motion, the issuing court must quash or modify a subpoena that:

(i) fails to allow a reasonable time to comply;

(ii) requires a person who is neither a party nor a party's officer to travel more than 100 miles from where that person resides, is employed, or regularly transacts business in person — except that, subject to Rule 45(c)(3)(B)(iii), the person may be commanded to attend a trial by traveling from any such place within the state where the trial is held;

(iii) requires disclosure of privileged or other protected matter, if no exception or waiver applies; or

(iv) subjects a person to undue burden.

(B) *When Permitted.* To protect a person subject to or affected by a subpoena, the issuing court may, on motion, quash or modify the subpoena if it requires:

(i) disclosing a trade secret or other confidential research, development, or commercial information;

(ii) disclosing an unretained expert's opinion or information that does not describe specific occurrences in dispute and results from the expert's study that was not requested by a party; or

(iii) a person who is neither a party nor a party's officer to incur substantial expense to travel more than 100 miles to attend trial.

(C) *Specifying Conditions as an Alternative.* In the circumstances described in Rule 45(c)(3)(B), the court may, instead of quashing or modifying a subpoena, order appearance or production under specified conditions if the serving party:

(i) shows a substantial need for the testimony or material that cannot be otherwise met without undue hardship; and

(ii) ensures that the subpoenaed person will be reasonably compensated.

**(d) Duties in Responding to a Subpoena.**

(1) *Producing Documents or Electronically Stored Information.* These procedures apply to producing documents or electronically stored information:

(A) *Documents.* A person responding to a subpoena to produce documents must produce them as they are kept in the ordinary course of business or must organize and label them to correspond to the categories in the demand.

(B) *Form for Producing Electronically Stored Information Not Specified.* If a subpoena does not specify a form for producing electronically stored information, the person responding must produce it in a form or forms in which it is ordinarily maintained or in a reasonably usable form or forms.

(C) *Electronically Stored Information Produced in Only One Form.* The person responding need not produce the same electronically stored information in more than one form.

(D) *Inaccessible Electronically Stored Information.* The person responding need not provide discovery of electronically stored information from sources that the person identifies as not reasonably accessible because of undue burden or cost. On motion to compel discovery or for a protective order, the person responding must show that the information is not reasonably accessible because of undue burden or cost. If that showing is made, the court may nonetheless order discovery from such sources if the requesting party shows good cause, considering the limitations of Rule 26(b)(2)(C). The court may specify conditions for the discovery.

(2) *Claiming Privilege or Protection.*

(A) *Information Withheld.* A person withholding subpoenaed information under a claim that it is privileged or subject to protection as trial-preparation material must:

(i) expressly make the claim; and

(ii) describe the nature of the withheld documents, communications, or tangible things in a manner that, without revealing information itself privileged or protected, will enable the parties to assess the claim.

(B) *Information Produced.* If information produced in response to a subpoena is subject to a claim of privilege or of protection as trial-preparation material, the person making the claim may notify any party that received the information of the claim and the basis for it. After being notified, a party must promptly return, sequester, or destroy the specified information and any copies it has; must not use or disclose the information until the claim is resolved; must take reasonable steps to retrieve the information if the party disclosed it before being notified; and may promptly present the information to the court under seal for a determination of the claim. The person who produced the information must preserve the information until the claim is resolved.

(e) *Contempt.* The issuing court may hold in contempt a person who, having been served, fails without adequate excuse to obey the subpoena. A nonparty's failure to obey must be excused if the subpoena purports to require the nonparty to attend or produce at a place outside the limits of Rule 45(c)(3)(A)(ii).

UNITED STATES DISTRICT COURT OF THE  
SOUTHERN DISTRICT OF WEST VIRGINIA  
CHARLESTON DIVISION

Kathy McCornack, et al.

THIS DOCUMENT RELATES TO:

Plaintiffs,

Case No.: 2:09-cv-0671

vs.

*Related MDL Case No.: 2:08-md-1968*

Actavis Totowa, LLC, et al.

Defendants.

**AMENDED NOTICE TO TAKE VIDEOTAPED ORAL DEPOSITION AND REQUEST  
FOR PRODUCTION AND COPYING OF DOCUMENTS AT THE DEPOSITION**

TO ALL PARTIES AND TO THEIR ATTORNEYS OF RECORD:

**PLEASE TAKE NOTICE** that, under Federal Rules of Civil Procedure 26(d), 30 and 45, Plaintiffs will take the deposition of **DR. WILLIAM L. GALANTER** on **Wednesday, August 3, 2011 at 10:00 a.m.** at MJ Reporting, 10 North Martingale Road, Schaumburg, IL 60173, (847) 619-7155.

The oral examination will continue from day to day until completed. This deposition will be recorded stenographically, may be recorded on videotape and will comply with any relevant orders in this litigation, including Pretrial Order No. 22, attached hereto as Exhibit A. This deposition is noticed in the above-captioned matter for any and all purposes permitted by the Federal Rules of Civil Procedure and any other federal, state, or local rules that apply to this action and the deposition will be taken in accordance with these rules. A copy of the subpoena duces tecum to appear and testify at a hearing or trial in a civil case is attached hereto as Exhibit

B and served herewith. Pursuant to Federal Rule of Civil Procedure 30(b)(2) and 45(a),

Plaintiffs request that Dr. Galanter produce for inspection at the time of deposition:

1. The witness' current curriculum vitae or resume.
2. All correspondence and communication between the witness or anyone acting on the witness' behalf, and attorneys representing defendants in this and the MDL Digitek® litigation.
3. All other documents prepared by the attorneys for the defendants and sent to the witness.
4. All documents, including documents and deposition transcripts which refer or relate to this and the MDL Digitek® litigation that the witness received from any source.
5. All retainer agreements or other agreements under which the witness has been or will be paid for work related to this and the related MDL Digitek® litigation.
6. All bills that the witness has rendered to attorneys and law firms in connection with this and the MDL Digitek® litigation.
7. A copy of the witness' entire file, including all electronic documents, and correspondence, in connection with this and the MDL Digitek® litigation.
8. All documents, including additional materials received or reviewed, tangible things, data, or writings that relied upon, examined, considered, or rejected in preparing the reports in this and the MDL Digitek® litigation, or subsequent to preparing his report.
9. Everything the witness reviewed that indicates any person may have ingested defective Digitek®.

10. All notes that the witness has taken in connection with review of this and the MDL Digitek® litigation matters.
11. All documents that the witness has prepared concerning the subject matter of this and the MDL Digitek® litigation.
12. All medical, scientific or other literature on which the witness relies in connection with the opinions expressed in his expert report.
13. All documents, tangible things, data, or writings concerning whether a Digitek® tablet that may have been adulterated may have ever been received by a pharmacist or consumer. This request is not limited to just the Digitek® tablets recalled in 2008 by Defendant Actavis, but to all Digitek® tablets that may have ever been received by a pharmacist or consumer and suspected to be adulterated for any reason.
14. All documents the witness reviewed in preparation for this deposition.

Respectfully Submitted:

Dated: July 28, 2011

/s/ Terry Kilpatrick  
Terry Kilpatrick (Calif. Bar No. 163197)  
Attorneys for Plaintiffs  
Ernst Law Group  
1020 Palm Street  
San Luis Obispo, CA. 93401  
Tel: 805-541-0300  
Fax: 805-541-5168  
E-mail: tk@ernstlawgroup.com

**CERTIFICATE OF SERVICE**

I hereby certify that on July 28, 2011, I or an employee under my control electronically filed the foregoing document with the Clerk of Court using the CM/ECF system, which will send notification of such filing to all counsel of record.

Dated: July 28, 2011

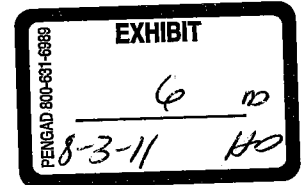
/s/ Terry Kilpatrick  
Terry Kilpatrick (Calif. Bar No. 163197)  
Attorneys for Plaintiffs  
Ernst Law Group  
1020 Palm Street  
San Luis Obispo, CA. 93401  
Tel: 805-541-0300  
Fax: 805-541-5168  
E-mail: tk@ernstlawgroup.com



**NMS Labs**  
3701 Welsh Road, PO Box 433A, Willow Grove, PA 19090-0437  
Phone: (215) 657-4900 Fax: (215) 657-2972  
e-mail: nms@nmslabs.com  
Robert A. Middleberg, PhD, DABFT, DABCC, Laboratory Director

**CONFIDENTIAL**

June 24, 2008



**TO:** 60C  
Santa Cruz County Coroner  
Attn: Alan Burt  
701 Ocean Street, #340  
Santa Cruz, CA 95060

**SUPPLEMENTAL TOXICOLOGY REPORT OF:**

NMS Workorder No:  
NMS Control No:  
Client ID No:

**McCORNACK, Daniel E.**  
08095896  
10843208  
08-0279

45/M

**SPECIMENS:** One gray top tube containing ~ 10 mL of peripheral blood, one clear vial containing ~ 14 mL of peripheral blood and two white plastic containers (one containing ~ 30 mL of urine and one containing ~ 32 g of liver) were received on 03/28/08.

**EXAMINATION:** Analysis Requested - Panel 8092B - Autopsy Toxicology Therapeutic and Abused Drug Screen  
Test No, 1615B - Digoxin

**FINDINGS:**

**Blood**

ETHYL ALCOHOL (by Enzymatic Assay & Headspace GC)	48 mg/dL (BAC=0.048 % w/v)
DILTIAZEM (by GC & GC/MS)	630 nanog/mL
DIGOXIN (by LC-MS/MS)	3.6 nanog/mL
QUINIDINE/QUININE* (by GC/MS)	Trace
ATROPINE (by GC/MS)	Positive

\*Quinine and quinidine can be differentiated analytically, but this is a separate analysis. If further delineation is necessary, please contact the laboratory.

**Incidental findings by GC/MS: CAFFEINE and THEOBROMINE.**

Other than the above findings, examination of the specimens submitted did not reveal any positive findings of toxicological significance by procedures outlined in the accompanying Analysis Summary.

*Handwritten signature and date: 6-27-08*

CONFIDENTIAL

NMS Workorder No: 08095896  
NMS Control No: 10843208  
Client ID No: 08-02790  
Page 2 of 3

**COMMENTS:**

1. Ethyl alcohol is a CNS-depressant and has effects so-related, e.g., impaired judgment, alertness and coordination.

If the determined blood alcohol concentration (BAC) is representative of the circulating BAC at the time of the fatal incident, then it represents as absorbed body burden of approximately 2 "drinks" of an alcoholic beverage in an adult of average size weighing approximately 155 lbs.

Note: a "drink" = 1 oz. of distilled spirits  
4 oz. of wine  
12 oz. of beer

Each of the drinks listed above contains about the same amount of ethyl alcohol.

2. Diltiazem (Cardizem®) is a calcium channel blocking coronary vasodilator indicated for the treatment of variant, exertional and unstable angina. It is also used in arrhythmic and/or hypertensive therapy. Desacetyldiltiazem is an active metabolite of diltiazem. Divided doses up to 180-360 mg daily may be prescribed for angina.

Therapeutic blood levels of diltiazem appear to be in the range of 50 to 200 nanog/mL. Numerous cases of diltiazem overdose have been reported. The majority of individuals who receive prompt treatment survive diltiazem overdose; however, death has been reported, especially in conjunction with other substances. Diltiazem has been found mixed with cocaine, either as a cutting agent or in an attempt to reduce cocaine-induced increased blood pressure. In a separate, small series of diltiazem related fatalities, the postmortem blood concentrations range from 6700 to 33,000 nanog/mL (mean 16,000 nanog/mL). In addition, diltiazem is reported to undergo postmortem redistribution with an average heart blood/femoral blood ratio of 2.6.

3. Digoxin (Lanoxin®) is a cardiac glycoside used in the treatment of congestive heart failure and other contractility-related deficiencies. There is considerable individualization of the dose of this medication and what is therapeutic in one individual may be toxic in another.

Individuals are generally titrated to find an appropriate dosage, especially since digoxin has a low therapeutic index.

4. Quinine and quinidine are stereoisomers derived from the bark of the cinchona tree. Quinine has been used in the past as an antimalarial, but is more commonly used today to treat muscle cramps. It is also used as a flavoring agent in tonic waters and as a cutting agent adulterant in illicit street drug dosages of heroin. Adverse effects include gastrointestinal disturbances, tinnitus, dizziness, arrhythmias and hypotension.

Quinidine is frequently used as an antiarrhythmic agent. It is available for acute administration by intramuscular or intravenous injection of 200 to 750 mcg or for maintenance therapy in oral doses of 600 to 4,000 mg daily. Toxicity is manifested by gastrointestinal disturbances, giddiness, tinnitus, diplopia and hypotension.

5. Atropine is an anticholinergic alkaloid used in pre-anesthetic therapy to control airway secretions and as an antispasmodic to control gastrointestinal spasms. It is frequently used as an antidote in the treatment of anticholinesterase-type pesticides. It can be obtained naturally from deadly nightshade or jimson weed. Atropine is also used in resuscitative attempts.

Toxic effects of atropine have considerable individual variation; however, at high doses, signs and symptoms include mydriasis, hot dry reddened skin, deliriums and hallucinations.

In resuscitative failure, most of the administered drug remains confined to the intravascular injection pathway.



NMS Labs  
3701 Welsh Road, PO Box 433A, Willow Grove, PA 19090-0437  
Phone: (215) 657-4900 Fax: (215) 657-2972  
e-mail: nms@nmslabs.com  
Robert A. Middleberg, PhD, DABFT, DABCC, Laboratory Director

CONFIDENTIAL

May 29, 2009

RECEIVED

TO: M60112  
Ernst & Mattison  
1020 Palm Street  
San Luis Obispo, CA 93401

JUN 04 2009

ERNST & MATTISON

CRIMINALISTICS REPORT OF:  
NMS Workorder No:  
Client ID No:

McCORNACK SR., Daniel Elwin  
09107925  
Not Provided

SPECIMENS: Item 1 One clear plastic container containing one white pill monogrammed "B-146"

The above evidence was received from United Parcel Services on 05/14/09.

EXAMINATION: Analysis Requested – Test No. 7011 – Special Request for Digoxin

FINDINGS:

Item 1

DIGOXIN  
(by LC-MS/MS)

0.250 mg/tablet

WEIGHT

113.79 mg

THICKNESS

Not measured due to pill being broken

Respectfully,

Matthew McMullin, MS, DABFT  
Forensic Toxicologist

MMM/sdw

This analysis was performed under chain of custody. The chain of custody documentation is on file at NMS Labs.

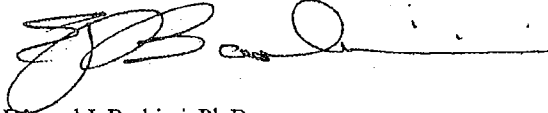
The remainder of the submitted specimens are scheduled to be returned/discarded six (6) weeks from the date of this report unless alternate arrangements are made by you prior thereto.

6-3

**CONFIDENTIAL**

NMS Workorder No: 08095896  
NMS Control No: 10843208  
Client ID No: 08-02790  
Page 3 of 3

Respectfully,



Edward J. Barbieri, Ph.D.  
Forensic Toxicologist

EJB/lfb

This analysis was performed under chain of custody. The chain of custody documentation is on file at NMS Labs.

Unless alternate arrangements are made by you, the remainder of the submitted specimens will be discarded six (6) weeks from the date of this report; and generated data will be discarded five (5) years from the date of this report.

\*\*\*\* ANALYSIS SUMMARY \*\*\*\*

**8092B - Therapeutic and Abused Drug Screen**

Test No. 8092B -- Drug Screen by Enzyme-Linked Immunosorbent Assay (ELISA) on Blood for: Amphetamine, Barbiturates, Benzodiazepines, Cannabinoids (Marihuana), Cocaine/Metabolites, Methamphetamine, Opiates and Phencyclidine (PCP); Headspace Gas Chromatography for Ethanol, Methanol, Acetone and Isopropyl Alcohol.

Test No. 8092B - Drug Screen II- Gas Chromatography and Gas Chromatography/Mass Spectrometry Analysis on Blood:

The following is a general list of compound classes included in the Gas Chromatographic screen. Other specific compounds outside these classes are also included. Please note that not all known compounds included in each specified class or heading are included. The detection of any particular compound is concentration-dependent. For a detailed list of all compounds included in this screen, please contact NMS Labs.

Analgesics (opioid and non-opioid), Anesthetics, Antiasthmatic Agents, Anticholinergic Agents, Anticonvulsant Agents, Antidepressants, Antiemetic Agents, Antihistamines, Antiparkinsonian Agents, Antipsychotic Agents, Antitussive Agents, Anxiolytics (Benzodiazepine and others), Cardiovascular Agents (non-digitalis), Hallucinogens, Hypnotosedatives (Barbiturate and others), Muscle Relaxants, Non-Steroidal Anti-Inflammatory Agents (excluding Salicylate) and Stimulants (Amphetamine-like and others).

Test No. 8092B - Colorimetric Analysis on Blood for: Salicylates and Acetaminophen.

Test No. 5010B - Alcohol Confirmation - Enzymatic Assay on Blood for: Ethanol (Ethyl alcohol).

Test No. 1640B - Diltiazem - Gas Chromatography on Blood for: Diltiazem.

Test No. 1615B - Digoxin - Liquid Chromatography - Tandem Mass Spectrometry on Blood for: Digoxin.

\*\*\*\*\* END OF REPORT \*\*\*\*\*

**CONFIDENTIAL**

NMS Workorder No: 09107925  
Client ID No: Not Provided  
Page 2 of 2

\*\*\*\*\***ANALYSIS SUMMARY**\*\*\*\*\*

Test No. 7011 – Special Request - Liquid Chromatography – Tandem Mass Spectrometry on Pills for: Digoxin.

\*\*\*\*\***END OF REPORT**\*\*\*\*\*

6-5



NMS Labs  
3701 Welsh Road, PO Box 433A, Willow Grove, PA 19090-0437  
Phone: (215) 657-4900 Fax: (215) 657-2972  
e-mail: nms@nmslabs.com  
Robert A. Middleberg, PhD, DABFT, DABCC, Laboratory Director

CONFIDENTIAL

September 22, 2009

RECEIVED

SEP 25 2009

ERNST & MATTISON

TO: M60112  
Ernst & Mattison  
Attn: Terry Kilpatrick  
1020 Palm Street  
San Luis Obispo, CA 93401

**SUPPLEMENTAL CRIMINALISTICS REPORT OF:** McCORNACK SR., DANIEL ELWIN  
NMS Workorder No: 09154008  
Client ID No: Prior NMS Workorder No: 09107925

**SPECIMENS:** Item 1 Five white pills in a Cinnamon Altoids® container.

The above evidence was received from United State Postal Service Priority Mail on 07/13/09.

**EXAMINATION:** Analysis Requested – Test No. 7011 – Special Request for Digoxin

**FINDINGS:**

Item 1.a

DIGOXIN (by LC-MS/MS)	0.247 mg/pill
WEIGHT	122.939 mg
THICKNESS	3.28 mm

Item 1.b

DIGOXIN (by LC-MS/MS)	0.244 mg/pill
WEIGHT	127.597 mg
THICKNESS	3.56 mm

Item 1.c

DIGOXIN (by LC-MS/MS)	0.227 mg/pill
WEIGHT	129.432 mg
THICKNESS	3.59 mm

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NMS Workorder No: 09154008  
Client ID No: Prior NMS Workorder No: 09107925  
Page 2 of 2

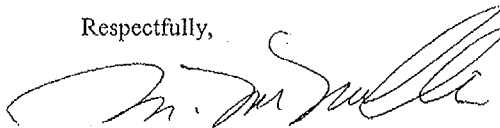
Item 1.d

DIGOXIN (by LC-MS/MS)	0.227 mg/pill
WEIGHT	128.525 mg
THICKNESS	3.54 mm

Item 1.e

DIGOXIN (by LC-MS/MS)	0.261 mg/pill
WEIGHT	127.690 mg
THICKNESS	3.52 mm

Respectfully,



Matthew McMullin, MS, DABFT  
Forensic Toxicologist

MMM/sdw

This analysis was performed under chain of custody. The chain of custody documentation is on file at NMS Labs.

The remainder of the submitted specimens are scheduled to be returned/discarded six (6) weeks from the date of this report unless alternate arrangements are made by you prior thereto.

\*\*\*\*\* ANALYSIS SUMMARY \*\*\*\*\*

Test No. 7011 – Special Request – Liquid Chromatography – Tandem Mass Spectrometry on Pill for: Digoxin.

\*\*\*\*\* END OF REPORT \*\*\*\*\*

CVS CareMark  
Recall Letter



May 2008

Dear Plan Participant:

You recently received a letter from CVS Caremark about the Digitek® (digoxin tablets, USP) 0.125 mg and Digitek (digoxin tablets, USP) 0.25 mg Patient Level Recall. We are providing you with an important update.

Please be aware that as a result of this recall, there is a market-wide shortage of digoxin. In an effort to meet the needs of all plan participants, enclosed is a maximum of a 45-day supply of replacement product.

***What to Do with Your Digitek***

For your safety and to ensure proper disposal, we have provided you with a return envelope. Please send your Digitek tablets to CVS Caremark in the original prescription bottle, if possible.

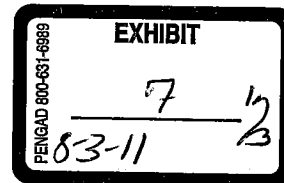
We encourage you to contact your provider with any questions or concerns regarding continuation of therapy.

Sincerely,

CVS Caremark

Enclosure

For more information on this issue you may contact the U.S. Food and Drug Administration (FDA) consumer inquiry line toll-free at 1-888-INFO-FDA (1-888-463-6332) or by accessing the FDA Web site at [www.fda.gov](http://www.fda.gov).



This page contains references to brand-name prescription drugs that are trademarks or registered trademarks of pharmaceutical manufacturers that are not affiliated with CVS Caremark.  
Your privacy is important to us. Our employees are trained regarding the appropriate way to handle your private health information.  
105-14158q

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